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Answer Key appears on page e63.

Placental Transfusion: Current Practices and Future Directions

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Education Gaps

1. Clinicians should be aware of the professional guidelines regarding cord clamping.
2. Clinicians should be aware of the benefits of placental transfusion on iron status during the first year of age.

Abstract

Over the past decade, the benefits of placental transfusion have been established in neonates. The evidence for this practice in various groups of newborns is reviewed. In addition, multiple professional organizations have recently issued guidelines for delayed cord clamping and cord milking. These recommendations are discussed.

Objectives

After completing this article, readers should be able to:

1. Describe the role of placental transfusion in the transition from fetal to neonatal circulation.
2. Explain the differences between delayed cord clamping, umbilical cord milking, and umbilical cord milking from a cut umbilical cord.
3. Recognize the benefits of placental transfusion on iron stores during the first year of age.

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ABBREVIATIONS

C-UCM	cut umbilical cord milking
DCC	delayed cord clamping
IVH	intraventricular hemorrhage
UCM	umbilical cord milking

INTRODUCTION

Since the last *NeoReviews* article on delayed cord clamping (DCC) published in 2015, new recommendations have been made on the use of DCC (Table 1), changing the indications for DCC, and providing new data on short- and long-term outcomes for infants who underwent DCC. (1)(2) Recent studies support previous research on the benefits of placental transfusion to the neonate. The benefits include improved cardiopulmonary transition, improved hematologic status, and improved iron stores. Current research focuses on alternative methods to provide placental transfusion such as umbilical cord milking

TABLE 1. **Recommendations for Delayed Cord Clamping and Cord Milking**

ORGANIZATION (YEAR)	RECOMMENDATION
World Health Organization (2014)	Delayed umbilical cord clamping (not earlier than 1 minute after birth) for improved maternal and infant health and nutrition outcomes.
Neonatal Resuscitation, 7th ed (2016)	Clamping should be delayed for at least 30–60 seconds for most vigorous term and preterm newborns.
Helping Babies Breathe, 2nd ed (2016)	Clamping should occur 1–3 minutes after birth. If possible, ventilation can be assisted with intact cord.
The American College of Obstetricians and Gynecologists (2017)	Delayed umbilical cord clamping in vigorous term and preterm infants for at least 30–60 seconds after birth.
American Academy of Pediatrics (2017)	Endorses the American College of Obstetricians and Gynecologists statement (2017)

(UCM) with the cord attached to the placenta, cutting the umbilical cord at more than 20 cm followed by milking the cord (C-UMC), and beginning resuscitation during DCC.

PLACENTAL TRANSFUSION AND TRANSITION

If the umbilical cord is left unclamped for a short time after the birth, some of the blood from the placenta passes to the infant (this is called *placental transfusion*) to increase the infant's blood volume and help the flow of blood to the infant's important organs including the lungs.

The transition from fetal to neonatal circulation involves major cardiovascular changes. Before birth, the placental circulation receives a high proportion of total fetal cardiac output, contributing a majority of venous return and preload to the fetal heart. As the lungs inflate postnatally, the partial pressure of oxygen increases, resulting in a drop in pulmonary vascular resistance and redirection of right ventricular blood flow to the lungs. The gradual increase in pulmonary blood flow allows for more oxygenated blood to return to the left atrium, and the increased volume provides preload to increase left atrial pressure. This increase in left atrial pressure closes the foramen ovale and increases left ventricular blood flow.

Placental transfusion is the process of allowing blood to flow from the placenta to the newborn for a short time after birth. During this time, the umbilical cord remains intact to provide placental transfusion as the healthy infant initiates breathing. The change in respiratory function from placenta to lungs is linked to a transfer of blood volume from the placenta to the neonate to maintain circulatory equilibrium as the pulmonary vascular bed opens. Through this process, there is a gradual transition from fetal to neonatal circulation with minimal alteration in cerebral blood flow. (3)(4)

DCC contributes roughly 24 mL/kg (95% confidence interval, 19–32 mL/kg) of birthweight to the neonatal blood volume, which is approximately 30% (24%–40%) of the total neonatal blood volume. (5) Farrar and colleagues found that it took 2 minutes for the net flow from the placenta to the infant to stop, but could take as long as 5 minutes. (6) Although many studies explored set times (30 seconds to 5 minutes) for cord clamping, the ideal timing of cord clamping is likely different for every newborn based on how the placental circulation fills the newly opened pulmonary vascular bed. Because of the high proportion of blood in the placental circulation, preterm infants are at higher risk of developing hypovolemia as a result of early cord clamping. This relative hypovolemia caused by early cord clamping leads to decreased oxygen delivery and can result in end organ ischemia.

Fetal cord blood is a rich source of hematopoietic stem cells that are vital for hematologic and immunologic development. (7)(8) The hematopoietic progenitor cells of umbilical cord blood have more proliferative capabilities than bone marrow. (9) Some authors suggest that DCC is nature's first stem cell transplant. (10) Currently, investigators are conducting preclinical and clinical trials using umbilical cord stem cells in the treatment of neonatal encephalopathy. (11)(12)

UMBILICAL CORD MILKING

In 2008, Hosono and colleagues published the results of their randomized controlled trial on 40 preterm infants who underwent UCM versus those who had early cord clamping. (13) Infants in the UCM group were placed at or below the level of the placenta while about 20 cm of the umbilical cord was vigorously milked toward the infant 2 to 3 times before clamping the cord. The investigators found that UCM resulted in higher hemoglobin, higher blood pressure, fewer blood transfusions, and improved respiratory status compared with early clamping without cord milking. (13)

There was no increase in indirect hyperbilirubinemia. March and colleagues reported similar findings in 113 preterm infants randomized to UCM (milking 20 cm of cord 3 times before clamping) or early cord clamping. They also reported that infants in the UCM group were less likely to develop an intraventricular hemorrhage (IVH). (14)

Another option for increasing neonatal blood volume is cut umbilical cord milking (C-UCM) in which the umbilical cord is cut early but more than 20 cm of the cord is left attached. The neonatal team can then milk the cord while the infant is resuscitated. This allows the neonatal team to initiate resuscitation while still providing placental transfusion. The Hosono group compared 20 preterm infants who underwent UCM with 20 infants in whom they cut the cord at 30 cm and transferred the infants to the neonatal team where the cord was milked once. Although this was not a randomized controlled trial, the authors found no differences between milking the cord while attached to the placenta versus cutting the cord and milking it once. (15) This finding suggests that C-UCM could be a potential strategy for providing placental transfusions to infants who require immediate resuscitation.

DCC VERSUS UCM

There has been a great deal of interest in UCM versus DCC. UCM can be completed quickly (within 20 seconds), (16) allowing for the neonatal team to begin the initial steps of resuscitation (Table 2). Rabe and colleagues randomized 58 infants born at less than 33 weeks' gestation to DCC or UCM, and found no differences between the groups in their hemoglobin concentrations or number of blood transfusions. (17) Katheria and colleagues compared DCC directly with UCM and found no difference between the groups in preterm infants who were born vaginally. (16) However, preterm infants born via cesarean delivery in the UCM group had higher hemoglobin levels at birth, higher superior vena cava flow, and right ventricular output in the first 12 hours, and increased urine output and blood pressure in the first 24 hours. (16) These findings suggest that UCM may have unique benefits for infants born via cesarean. UCM may lead to a greater placental transfusion, but the data to suggest that this greater transfusion results in better outcomes are limited.

CONCERNS WITH DCC AND UCM

Although the cardiopulmonary and hematologic benefits of DCC and UCM are extensive, there are still some concerns. (18) Previous studies concluded that the volume of blood transfused was dependent on the position of the newborn in relation to the placenta. Vain and colleagues challenged these findings in a study on the position of the newborn relative to the placenta before cord clamping. (19) His group randomized 546 singleton newborns either to the group held at the introitus or the group placed on the mother's abdomen or chest during 2 minutes of DCC, and found no differences in the volume of blood transfused (mean volume gained 56 g [introitus] vs 53 g [abdomen]). (19) They concluded that positioning of the newborn before cord clamping did not significantly affect the volume of transfusion.

There is also concern that DCC or UCM could potentially transfer too much blood to the neonate, resulting in hyperviscosity when hemoconcentration occurs in the first few hours after birth. Preterm infants are less susceptible to developing hyperviscosity after a placental transfusion than are term neonates because of lower serum protein concentrations, greater erythrocyte deformability, and lower hematocrit counts. (20) Although preterm erythrocytes are larger than those of term neonates, they are more elastic and therefore less prone to hyperviscosity. In a recent study, Christensen and colleagues found that peak viscosity values measured in the 12 hours after UCM were below the 12cP range previously used to define hyperviscosity in term neonates. (21) Mercer and colleagues found that term infants with 5 minutes of DCC or UCM 5 times had higher hematocrit counts and higher hemoglobin levels at 24 to 48 hours of age, with no increase in jaundice, symptomatic polycythemia, or other adverse effects. (22) In meta-analyses, there were no differences in the incidence of symptomatic polycythemia in term infants who had early or late cord clamping. (23)

DCC and UCM raise concerns for increased neonatal jaundice requiring phototherapy. The 2012 meta-analysis by McDonald et al showed that term infants who had DCC had a significantly higher risk of requiring phototherapy; however, the risk difference was noted to be small, at less than 2%, and no difference was noted in the need for exchange transfusion. (23) In a 2012 meta-analysis, Rabe et al showed that preterm infants who had DCC or UCM had an increase in peak bilirubin levels and a nonsignificant trend toward the need for increased phototherapy. (17)

IRON BENEFITS

Preterm delivery results in decreased transfer of iron from the pregnant woman to the fetus, because this transfer occurs predominantly during the third trimester of pregnancy. After birth, preterm infants continue to develop an iron deficiency because of blood loss from laboratory sampling. Iron deficiency during early infancy is associated with long-term neurodevelopmental impairments that seem to

TABLE 2. **Studies Evaluating Delayed Cord Clamping versus Cord Milking**

STUDY	POPULATION/METHODOLOGY	DCC (N)	UCM (N)	OUTCOMES
Rabe et al (17)	58 preterm infants<33 completed weeks of gestation Randomized to DCC for 30 seconds or UCM ×4	31	27	Mean hemoglobin values for each group at 1 hour after birth were similar. There was no significant difference in number of neonates undergoing transfusion.
Jaiswal et al (24)	200 infants >36 weeks UCM was done on 25 cm of cord length Clamping delayed by 60–90 seconds in DCC group	100	100	DCC and UCM had similar effect on cerebral blood flow velocities and Doppler indices in MCA
Katheria et al (16)	23 0/7 to 31 6/7 weeks' GA, stratified by GA and mode of delivery (C/S or VD) Randomized to UCM ×4 or 45–60 seconds DCC	79 C/S	75 C/S	No difference between groups in those delivered VD The UCM group delivered by C/S had higher superior vena cava flow and right ventricular output in the first 12 hours of life, higher hemoglobin level, higher delivery room temperature, higher blood pressure over the first 15 hours, and greater urine output in the first 24 hours of life.
Vatansever et al (25)	189 term infants Randomized to either early clamping, DCC, or DCC + UCM	ECC: 63 DCC: 63	DCC + UCM: 63	Measures of oxidative stress were greatest in infants who had ECC. There were no differences in measures of oxidative stress between DCC and UCM.

C/S=cesarean delivery; DCC=delayed cord clamping; ECC=early cord clamping; GA=gestational age; MCA=middle cerebral artery; UCM=umbilical cord milking; VD=vaginal delivery.

be irreversible. (27) A number of investigators have evaluated short-term iron stores in term and preterm infants who underwent DCC, UCM, or C-UCM, and found improved hemoglobin or ferritin levels at 6 weeks to 12 months of age (Table 3). (28)(29)(30)(32)(33)

Yadav and colleagues published a 3-arm study of 300 term infants. (31) The C-UCM group had the cord cut early at 25 cm and then the neonatal team milked the cord 3 times. The second group had DCC for 90 seconds after which the cord was cut at 2 to 3 cm and the infant transferred to the neonatal team. The third group had a 90-second delay, followed by cord cutting at 25 cm, and then the neonatal team milked the cord 3 times. DCC followed by cord milking resulted in the highest ferritin concentration at 6 weeks of age (296 ng/mL [665 pmol/L] in the DCC plus cord milking group compared with 269 ng/mL [604 pmol/L] in the DCC group and 185 ng/mL [416 pmol/L] in the cord milking group). (31)

Kc and colleagues randomized 540 late preterm and term infants to early cord clamping or DCC and monitored hematologic and iron indices at ages 8 and 12 months. (32) An increase in hemoglobin and a decreased incidence in iron deficiency anemia was noted in the DCC group at both these times, with a number needed to treat of 12 (Table 3). Overall, iron status improved and iron indices were higher in those infants who underwent DCC or UCM compared with infants who had early cord clamping. A recent meta-analysis of DCC in term infants found 5 trials (comprising 1,152 infants) reporting on iron deficiency anemia at 3 to 6 months of age. Infants who underwent DCC were significantly less likely to have iron deficiency. (23)

RESUSCITATION SIMULTANEOUS WITH DCC

DCC in infants who require resuscitation is currently being studied. Many providers are reluctant to delay resuscitation, specifically ventilation, in both term and preterm infants who are not vigorous at birth, perceiving that the infant needs immediate ventilation. This is evident in randomized studies on DCC in which 14% to 22% of infants randomized to DCC were clamped early due to provider concern. (5)(16)(22) However, there are increasing data to suggest that these infants may be the ones who benefit the most from DCC. In an observational study, Ersdal and colleagues in rural Tanzania found that healthy self-breathing neonates were more likely to die or be admitted if the umbilical cord is clamped

TABLE 3. **Placental Transfusion and Iron Stores**

STUDY	POPULATION	RANDOMIZATION (N)		OUTCOMES
Upadhyay et al (30)	>35 weeks' gestation infants Randomized to UCM or no UCM	C-UCM: 100	No UCM: 100	Mean hemoglobin and mean serum ferritin were significantly higher in the UCM group compared with the no UCM group at 6 weeks of age.
Andersson et al (26)	382 full-term infants Follow-up of iron status at 12 months (ferritin level, transferrin saturation, transferrin receptor level, reticulocyte hemoglobin level, and mean cell volume)	DCC: 193	ECC: 189	DCC (174 at follow-up) and ECC (163 at follow-up) groups did not differ in iron status at 12 months
Bora et al (28)	200 term infants Randomized to C-UCM group (umbilical cord was clamped at 40-cm length and milked) or control group (cord clamped at 5 cm and not milked)	C-UCM: 100	ECC: 100	Mean hemoglobin concentration and ferritin at 6 months was higher in the C-UCM group than the control group (*P* = .004)
Yadav et al (31)	300 term infants Randomized to UCM, DCC, or a combination of DCC plus C-UCM Iron stores evaluated at 6 weeks	DCC: 100 DCC+ C-UCM: 100	ECC: 100	Ferritin at 6 weeks was significantly higher in the group receiving both DCC and C-UCM compared with the group that had only UCM or only DCC DCC plus C-UCM improved iron stores at 6 weeks of age in term infants to a greater extent than either of the two interventions alone
Agarwal et al (33)	200 term infants Randomized at birth to undergo DCC for 60 to 90 seconds or C-UCM Outcome measures were iron status and physical growth parameters at 12 months	DCC: 100	C-UCM: 100	200 enrolled, 161 completed the follow-up. There were no differences in hemoglobin or ferritin between groups at one year In addition, there were no significant differences in growth measurements
Kc et al (32)	540 late preterm and term infants Randomized to DCC (≥180 seconds after delivery) or early clamping (≤60 seconds after delivery) Iron indices evaluated at ages 8 and 12 months	DCC: 270	ECC: 270	Infants in the DCC group had higher levels of hemoglobin and reduced prevalence of anemia and iron deficiency at 8 months. At 12 months, delayed cord clamping resulted in decreased risk for iron deficiency

C-UMC=umbilical cord milking with cut cord; DCC=delayed cord clamping; ECC=early cord clamping; UCM=umbilical cord milking.

before the onset of breathing. (34) The risk of death or admission decreased by 20% for every 10-second delay in cord clamping after the onset of spontaneous respirations. (34)

In preterm lamb studies, the lambs that underwent early cord clamping followed by assisted ventilation had large changes in heart rate, cardiac output, and both cerebral and arterial oxygenation during transition. Lambs that received ventilation before cord clamping had a smoother transition with smaller changes noted. (3)(35)(36)

Several small studies have investigated beginning resuscitation by assisting ventilation before clamping the cord. DCC appears to be more successful in studies in which assisting ventilation occurs during DCC. Winter and colleagues placed the newborn on the mother's abdomen during cesarean delivery or on a nearby table during vaginal deliveries while providing ventilation via a T-piece resuscitator, if needed, during the 90-second delay in cord clamping. (37) They reported that vaginal deliveries were more challenging, because the obstetrician was required to move aside to make room for the team. Although the protocol was feasible, the investigators did note that this approach required significant preparation and was not possible in precipitous deliveries. (37)

Katheria and colleagues conducted a randomized controlled trial providing DCC alone versus DCC plus ventilation to 150 preterm infants. (38) Although they found that ventilation during DCC was feasible, it had no effect on placental weight, neonatal hemoglobin levels, cardiac function (as assessed on echocardiography), and other physiologic variables in the first 24 hours after birth, or neonatal outcomes when compared with DCC and stimulation alone. (38) In another randomized controlled trial, the same investigators evaluated term newborns who were at risk of needing resuscitation to underwent DCC for 1 or 5 minutes. Infants randomized to 5-minute DCC were placed on the mother's abdomen if they were vigorous or placed on a bedside cart and ventilation was provided as needed. If the infant was randomized to the 1-minute DCC group, neonates were placed on the mother's abdomen if they were vigorous; however, if the infants were not vigorous, the cord was cut immediately to provide resuscitation. Although the numbers of infants receiving resuscitation were low in each group, there was a trend for less resuscitation and improved Apgar scores in the 5-minute DCC group. Infants in the 5-minute DCC group showed an increase in cerebral tissue oxygen saturation and decreased fractional cerebral tissue oxygen extraction as measured by near-infrared spectroscopy. (39) Although it is physiologically plausible and preclinical data support DCC in infants who require resuscitation, it remains to be seen if neonates have any clinical benefits. Several ongoing multicenter, randomized, controlled trials are currently exploring this topic.

DCC IN SELECT POPULATIONS

Most studies on DCC exclude infants with prenatally diagnosed anomalies; however, recently, some investigators have begun to evaluate DCC in these unique groups of neonates.

Backes and colleagues performed a pilot trial randomizing 30 infants with congenital heart disease to early cord clamping or DCC. They found the procedure to be feasible and resulted in a lower proportion of infants exposed to red blood cell transfusions during hospitalization. (40) Further research is needed to assess if there are long-term benefits to DCC in neonates with congenital heart disease.

Lefebvre and colleagues conducted a prospective, observational, single-center trial on 40 consecutive newborns with a prenatal diagnosis of congenital diaphragmatic hernia. They found it possible to initiate resuscitation during DCC and reported that DCC resulted in higher hemoglobin levels. In addition, they found Apgar scores at 1 and 5 minutes, pH at 1 hour after birth, and mean blood pressures were all higher in the group of infants resuscitated during DCC. Plasma lactate concentrations were lower at 1 hour after birth in the infants with intact cord resuscitation. The authors found no adverse neonatal outcomes in the infants who had DCC during resuscitation. (41)

Garabedian and colleagues looked specifically at a cohort of 72 infants who received an intrauterine transfusion for fetal anemia due to red blood cell alloimmunization. (42) Infants who underwent DCC had improved hemoglobin levels at birth, a longer delay in need for transfusion, decreased exchange transfusions, and no increase in severe indirect hyperbilirubinemia compared with infants who had immediate cord clamping at birth. (42)

NEURODEVELOPMENTAL OUTCOMES

Although hematologic and iron outcomes appear improved in infants undergoing DCC, neurodevelopmental outcomes after the newborn period are largely unknown. Rabe and colleagues conducted a randomized controlled trial comparing DCC to cord milking. (43) The original trial was not designed to assess neurodevelopmental outcomes but after conclusion of the trial, the authors invited families to participate in neurodevelopmental testing at 2 and 3.5 years of age. They were able to follow up 67% of the original cohort at 2 years and 50% at 3.5 years, and found no differences overall between the DCC and UCM groups.

Mercer and colleagues randomized 72 preterm infants to early cord clamping or DCC and followed them to 7 months' corrected age. (44) The investigators found that Bayley II Mental Developmental Index scores were similar between infants who had DCC and those who had early clamping. They found significant improvements in rates of IVH and late-onset sepsis in infants randomized to DCC. (44) In a subgroup analysis, they found that male infants with DCC had higher motor scores on the Bayley-II. (45) More recently, the same investigators conducted a larger trial of 208 preterm infants randomized to 30 to 45 seconds of DCC followed by a single cord milking, or early cord clamping at less than 10 seconds. DCC reduced the child's chance of scoring less than 85 on Bayley-III motor composite score by 68%. However, DCC did not alter the incidence of IVH or late-onset sepsis in preterm infants in this large study. The authors noted that the groups were unbalanced with respect to the indication for delivery, specifically infants who were born for maternal indications versus infants who were born due to preterm labor. Ongoing trials are expected to add further insight into how DCC and UMC affect neurodevelopmental outcome in preterm infants.

Iron deficiency anemia has been associated with impaired development. Andersson and colleagues conducted a large, randomized, controlled trial on healthy term infants who underwent DCC versus those who had immediate cord clamping. They found that DCC had significant effects on iron status at 4 months, with higher serum ferritin concentrations and less iron deficiency. (29) These infants were evaluated at 4 years of age and neurodevelopmental testing was conducted on 263 children (69% of those randomized at birth). DCC showed a trend toward improving process-speed quotient on the Wechsler Preschool and Primary Scale of Intelligence III (P=.06). Children who had DCC showed improved fine motor skills (P=.03) and improved personal-social skills (P=.006) as measured by the Ages and Stages Questionnaire. (46)

SUMMARY

A significant body of evidence exists to support the use of DCC and UCM. Early evidence suggests that C-UCM may have similar benefits, but further research is needed. Ongoing research is needed to assess the benefits of initiating resuscitation during DCC in term infants and in select populations.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the rationale, risks, and benefits of delayed cord clamping.

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1. You are preparing for a delivery of an infant at 29 weeks' gestational age. As you prepare the radiant warmer and other equipment and supplies, you consider the goals for the transition from fetal to neonatal circulation. Which of the following statements regarding this transition and delayed cord clamping (DCC) is correct?
   - A. DCC will lead to a relatively large increase (∼75%) in cerebral blood flow.
   - B. DCC will contribute roughly 24 mL/kg of birthweight to the neonatal blood volume.
   - C. In this infant, ∼30 seconds of DCC should allow for ∼99% of the net flow from placenta to infant, and cessation of DCC will ultimately occur before 1 minute in all infants.
   - D. If performed with adequate timing, the placental transfusion from DCC will provide ∼5% of the total neonatal blood volume.
   - E. Due to the preterm infant's relatively small size and blood volume, the length of time of DCC should be proportionately lower for infants of lower gestational age.
2. As part of a clinical trial, a preterm infant undergoes umbilical cord milking (UCM) at delivery. Which of the following results have been found in previous clinical trials for UCM compared with no milking?
   - A. Increased incidence of severe intraventricular hemorrhage.
   - B. Increased need for intubation in the delivery room.
   - C. Decreased incidence of severe hypothermia and decreased incidence of cold stress.
   - D. Decreased need for blood transfusions and higher blood pressure.
   - E. Increased incidence of renal thrombi and higher creatinine concentration during the first week.
3. Your team is implementing a policy for DCC for your delivery service. As you consider the policy, you are reviewing the potential risks of this policy in case parents ask about the practice. Which of the following have been found in previous studies and reviews?
   - A. There is large dependence on positioning of the newborn relative to the placenta before cord clamping, with infants placed slightly higher (ie, on the mother's abdomen) than the introitus level having about 50% less placental transfusion.
   - B. Compared with term infants, preterm infants are less susceptible to developing hyperviscosity after a placental transfusion.
   - C. Meta-analyses have shown that symptomatic polycythemia is more common in DCC for term and preterm infants, particularly if performed for more than 30 seconds.
   - D. Although still very rare, a statistically significant increase in exchange transfusions has been demonstrated with DCC.
   - E. No studies have shown an increased need for phototherapy for DCC relative to early clamping, either in preterm or term infant populations.
4. An infant born at 40 weeks' gestational age undergoes DCC at delivery and has a routine newborn course and is discharged from the hospital after 2 days. Compared with infants without DCC, what is observed in infants after receiving DCC?
   - A. Higher likelihood of hypoglycemia in the first 2 days.
   - B. Higher hemoglobin and ferritin levels at 6 weeks and 12 months of age.
   - C. No difference in incidence of iron deficiency anemia at 6 or 12 months of age.
   - D. Higher chance of hypoxic-ischemic encephalopathy.
   - E. Quicker time to crawling, walking, and speaking 10 words.
5. A 26-week gestational age infant is delivered by cesarean section. Although the intention was to provide DCC, the infant appears to have no respiratory effort at 5 seconds after delivery and the obstetrician requests that either the cord be clamped or the team begin

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resuscitation with positive pressure ventilation during DCC. Which of the following statements is most consistent with the current literature and guidelines?

A. As it is fairly easy to provide positive pressure ventilation to infants while DCC is occurring, this should be performed for most preterm infants starting at 5 seconds of age, including in this infant.
B. DCC is most optimal in both term and preterm infants if the cord is clamped before the onset of spontaneous respirations.
C. Although physiologically plausible and preclinical data exist to support DCC in infants who require resuscitation, it is not well established in demonstrating a consistent clinical benefit, and currently is not a recommended guideline.
D. Preterm infants receiving DCC for longer than 1 minute have been shown to have more adverse outcomes compared with those receiving DCC for less than 1 minute, regardless of the need for resuscitation, including lower 5-minute Apgar scores and higher chance of intraventricular hemorrhage.
E. The large majority of preterm infants will not have spontaneous respirations during DCC, regardless of the duration of DCC, ranging from 30 seconds to 5 minutes.

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Coagulation Disorders in the Newborn

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Education Gaps

1. Coagulation disorders in the newborn are a challenge to caregivers.
2. Abnormalities of the immature, complex coagulation system of the newborn can have life-threatening consequences.

Abstract

Coagulation disorders in the newborn are a challenge to caregivers. Abnormalities of the immature, complex coagulation system of the newborn can have life-threatening consequences. This review provides a summary of the most common newborn bleeding abnormalities faced by clinicians, as well as an approach to the diagnosis and management of these disorders.

Objectives

After completing this article, readers should be able to:

1. Interpret the initial results of laboratory screening in the bleeding neonate.
2. Distinguish between different causes of thrombocytopenia.
3. Recognize that there are various factor products available for the treatment of hemophilia.
4. Recognize that untreated vitamin K deficiency presents as late-onset vitamin K–dependent bleeding and carries a high risk of intracranial hemorrhage.
5. Determine the appropriate blood product to treat a newborn with a coagulopathy.

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ABBREVIATIONS

aPTT	activated partial thromboplastin time
DIC	disseminated intravascular coagulation
FFP	fresh frozen plasma
GT	Glanzmann thrombasthenia
ICH	intracranial hemorrhage
IgG	immunoglobulin G
INR	international normalized ratio
NAIT	neonatal alloimmune thrombocytopenia
PT	prothrombin time
TAM	transient abnormal myelopoiesis
VKDB	vitamin K–dependent bleeding
vWF	von Willebrand factor

INTRODUCTION

Bleeding in healthy neonates is rare. When it does occur in newborns, determining the exact cause can pose a challenge for practitioners because newborns have a continuously evolving coagulation system. The coagulation system is composed of various proteins produced by the liver and endothelial system. This pathway requires platelet activation to initiate hemostasis and set the foundation for factors to become activated.

Structurally, the platelets of premature and full-term neonates are similar to those of adults. Functionally, however, neonatal platelets are hyporeactive in response to multiple agonists in vitro, with more pronounced hyporeactivity noted in preterm infants. Compared with adult platelets, neonatal platelets contain higher levels of messenger RNA associated with protein synthesis and processing, while carrying significantly lower levels of genes involved in calcium transport/metabolism and cell signaling. (1) Thus, variation in the platelet transcriptome may be underlining the hypofunctional phenotype of neonatal platelets. Platelet reactivity increases with age, but the duration of hyporeactivity remains unclear. (2) Despite platelet hyporeactivity, in vivo global assays of platelet function, such as bleeding time and the platelet function analyzer, do not demonstrate platelet dysfunction. (3) Furthermore, thromboelastography and rotating thromboelastometry show that neonatal platelets have accelerated coagulation and strong clot firmness. These advantages are probably due to multiple factors including increased concentrations of von Willebrand factor (vWF), the presence of large vWF multimers, and the high volume of neonatal packed cells. (3)(4)(5)

In neonates, the differences in procoagulant factors are mainly quantitative. Procoagulant factors do not cross the placenta. The fetus produces these factors in utero and they reach measurable levels by 10 weeks' gestational age. These factors gradually mature functionally and quantitatively during the gestational period and after birth, and reach adult levels at approximately 6 months of age. Interestingly, low levels of coagulation factor in premature neonates are compensated by accelerated maturation, so that they also reach normal levels by age 6 months. It is important to keep in mind that low concentrations of coagulation factors will result in prolongation of baseline coagulation assays, particularly the activated partial thromboplastin time (aPTT). This is a normal finding in neonates, and it is therefore very important that laboratory results are interpreted in conjunction with age-adjusted normal ranges. Plasma levels of coagulation factor VIII, vWF, and fibrinogen in neonates should be close to or surpass adult levels. (6) Therefore, if values for these specific proteins are low during the newborn period, the clinician should evaluate the neonate for a deficiency, rather than waiting to see if normalization occurs at an older age.

LABORATORY APPROACH TO BLEEDING IN THE NEONATE

Initial screening investigations of a neonate with bleeding are usually composed of a complete blood count, aPTT, prothrombin time (PT), thrombin time, and fibrinogen level. It is also important to remember that factor XIII level should be measured in a neonate with significant intracranial hemorrhage (ICH) because factor XIII deficiency will not prolong the PT or aPTT. If the neonate's PT or aPTT is prolonged, additional 1:1 mixing studies may be needed. These studies involve repeat testing of the patient's plasma with normal plasma. If addition of normal plasma corrects the abnormality, it is likely that the patient has a deficiency of a compound in the added plasma.

Sampling problems are common in the newborn period, and it is particularly important that samples for coagulation testing avoid contamination or activation before analysis. Care should be taken to ensure proper filling of the citrated tube, because the ratio of plasma to citrate is key to reliable PT/aPTT results. As mentioned previously, published ranges of coagulation factors should be used to interpret results. Ideally, laboratories processing large numbers of neonatal samples should derive their own in-house reference ranges, because these are both machine and reagent specific. The high volume of neonatal packed red blood cells also results in a minor degree of spurious prolongation of coagulation times, and this is particularly relevant in polycythemic infants. In this case, the coagulation laboratory must be made aware of the neonate's elevated hematocrit, so that the technicians can adjust for low plasma volume and decrease the amount of citrate in the tube.

Results of basic coagulation screening can be interpreted as follows:

1. Prolonged aPTT and PT
   a. If the aPTT/PT normalizes with 1:1 mixing, consider vitamin K deficiency and liver disease. If these possibilities are not applicable clinically and the thrombin time is normal, this suggests defects of the common pathway (factors I, II, V, and X). An abnormal thrombin time suggests disorders of fibrinogen.
   b. If the aPTT/PT remains prolonged with 1:1 mixing, consider contamination with heparin.
   c. If the prolonged aPTT/PTT is associated with thrombocytopenia, consider disseminated intravascular coagulation (DIC).
2. Isolated prolongation of aPTT
   a. If the aPTT normalizes with 1:1 mixing, consider hemophilia A or B, as well as defects of factors XI and XII.
3. Isolated prolongation of PT
   a. If the PT normalizes with 1:1 mixing, consider vitamin K deficiency and congenital factor VII deficiency.
4. Isolated thrombocytopenia
   a. Differential includes neonatal alloimmune thrombocytopenia (NAIT) and autoimmune thrombocytopenia, an inherited platelet disorder.

5. All screening coagulation test results are normal, but the neonate is still bleeding
   a. Consider testing for factor XIII deficiency (associated with prolonged bleeding from umbilical stump).
   b. Consider vWF deficiency.
   c. Consider platelet function defect (may not present with thrombocytopenia).
   d. Consider defect in fibrinolytic pathway (eg, α_2-antiplasmin and plasminogen activator inhibitor 1 deficiency).

PLATELET DISORDERS: NEONATAL THROMBOCYTOPENIA

Thrombocytopenia in neonates is defined as a platelet count less than $150\times10^3/\mu L$ ($150\times10^9/L$). This hematologic abnormality is present in 1% to 5% of healthy newborns, with severe thrombocytopenia occurring in up to 50% of all newborns admitted to the NICU. (7) As previously mentioned, the structure of platelets in neonates is similar to that in adults, with a mean platelet volume ranging from 6 to 10 fL. Studies have shown that young platelets are typically larger than old platelets and are functionally more active. In general, a predominance of large platelets in a thrombocytopenic patient suggests compensatory release of young platelets from the bone marrow whereas the presence of small platelets indicates impaired platelet production in the bone marrow. (8) Nonetheless, inherited causes of thrombocytopenia must always be considered.

Fetal Alloimmune Thrombocytopenia and NAIT

Fetal alloimmune thrombocytopenia and NAIT are the most common causes of severe thrombocytopenia (9) and intracranial bleeding in term newborns, (10) with the majority occurring in utero. NAIT results from destruction of platelets by maternal immunoglobulin G (IgG) antibodies against paternally inherited platelet antigens (most commonly the PLA1 antigen) and can present in the fetal or neonatal period. The incidence of NAIT is approximately 1 in 1,000 live births. (11) Unlike Rh disease of the newborn, NAIT can affect both first and subsequent pregnancies, with 50% of cases presenting in the first pregnancy. Fetomaternal transfusions or fetomaternal hemorrhage during pregnancy results in the recognition of the paternal antigens and the creation of IgG antibodies that can cross the placenta. An infant born to a mother who previously gave birth to an infant with NAIT tends to have more severe disease than the older sibling, likely because of increased antibody production. (12) The degree of thrombocytopenia in NAIT can be severe, with platelet counts less than $10\times10^3/\mu L$ ($10\times10^9/L$) occurring in the first day after birth. The maternal platelet count will be normal; this is in contrast to the low maternal platelet count found in neonates with thrombocytopenia caused by maternal idiopathic thrombocytopenia purpura.

The diagnosis of NAIT requires identification of antibodies in maternal serum against the paternal platelet genotype or a mismatch of platelet genotype between the infant and the father or mother. Delays may be associated with serologic testing, and therefore, therapy in affected neonates should be initiated as soon as the diagnosis is suspected. Management includes transfusing the neonate with maternal platelets or random donor platelets. Administration of intravenous immunoglobulin can also increase the infant's platelet count and protect the transfused random donor platelets from maternal antibodies. Once the platelet count increases sufficiently (typically clinicians use a value $>50\times10^3/\mu L$ [$50\times10^9/L$]), treatment can be stopped; however, severe thrombocytopenia requiring transfusion therapy may recur until the maternal antibody concentration is significantly reduced.

If a neonate is suspected of having NAIT, it is extremely important that the mother is aware that her future pregnancies may be at risk of a more severe form of NAIT. The mother's obstetrician should also be alerted to this risk. Ideally, the infant's mother and father should have platelet antigen testing to confirm the diagnosis. If the diagnosis is confirmed or if there is a high suspicion of NAIT in a prior pregnancy, the obstetrician should monitor the mother's next pregnancy for intrauterine manifestations of NAIT that might require interventions.

Neonatal Autoimmune Thrombocytopenia

Neonatal autoimmune thrombocytopenia is caused by the placental transfer of maternal autoantibodies, and is found in infants of mothers with systemic lupus erythematosus, idiopathic thrombocytopenia purpura, or other autoimmune disorders. Maternal disease severity or maternal platelet count during pregnancy can be used to predict the level of severity in neonates. Fortunately, the clinical manifestations in neonates are less severe than in NAIT with the risk of ICH being less than 1%. (13) In all infants born to affected mothers, platelet counts should be obtained at birth and trends observed for the first few days to ensure that the nadir does not necessitate treatment with intravenous immunoglobulin or steroids. In general, the affected neonate's platelet count will start to rise by 7 days after birth, as the maternal antibody levels decrease.

Inherited Platelet Disorders

Inherited thrombocytopenia can be caused by various gene mutations and can be classified based on platelet size (Table 1). Neonates with an associated syndrome can have many

TABLE 1. **Classification and Characteristics of Congenital Thrombocytopenia Based on Platelet Size**

SIZE	
Small (mean platelet volume [MPV] <6 fL)	**Wiskott-Aldrich syndrome (WAS)** • X-linked; mutation in *WAS* gene • Eczema, thrombocytopenia (100% incidence), immunodeficiency • Increased risk of malignancy in childhood and adolescence • Hemorrhage in >80%. Ranges from epistaxis and petechiae to intestinal and intracranial bleeding **X-linked thrombocytopenia** • X-linked; mutation in *WAS* gene • Mild variant of WAS
Normal size (MPV 6-10 fL)	**Thrombocytopenia-absent radius (TAR) syndrome** • Microdeletion at chromosome band 1q21.1. Can be AR/AD, 25% de novo • Bilateral absence of radii, severe thrombocytopenia with platelet counts less than $50\times10^3/\mu L$ ($50\times10^9/L$) and the presence of both thumbs • More than 50% have severe thrombocytopenia in the first week after birth • Platelet counts improve over the 1st year and can recover spontaneously to near normal **Congenital amegakaryocytic thrombocytopenia (CAMT)** • Autosomal recessive; *MPL* mutations • Severe thrombocytopenia ($<10\times10^3/\mu L$ [$10\times10^9/L$]) at birth with absence of megakaryocytes in the bone marrow • Can progress to pancytopenia and leukemic transformation later in life **Radioulnar synostosis with amegakaryocytic thrombocytopenia (RUSAT)** • Gene mutation in *HOXA11* • Moderate-to-severe thrombocytopenia present at birth • Congenital fusion of the radius and ulna with limited pronation and supination of the forearm • Thrombocytopenia persists and may progress to hypocellularity and pancytopenia **Glanzmann thrombasthenia (GT)** • Autosomal recessive • Platelets contain defective/low levels of fibrinogen receptor GpIIb/IIIa • Bleeding is mostly mucocutaneous and can be moderate to severe • Platelet is normal as is morphology; but bleeding can manifest after birth **Familial platelet disorder with predisposition to myeloid malignancy** • Germline mutation in *RUNX1* gene • Mildly decreased thrombocytopenia with predisposition to malignancy
Large (MPV >10 fL)	**MYH9-related disorders (autosomal dominant; 35% are sporadic)** • *May-Hegglin anomaly*: mild-to-moderate thrombocytopenia with cytoplasmic inclusions (Dohle bodies) in peripheral blood leukocytes, also with sensorineural hearing loss • *Fechtner syndrome:* mild-to-moderate thrombocytopenia with cytoplasmic inclusions (Dohle bodies) in peripheral blood leukocytes, also with sensorineural hearing loss, cataracts, and renal disease • *Sebastian syndrome*: mild thrombocytopenia with cytoplasmic inclusions (Dohle bodies) in peripheral blood leukocytes, **without** sensorineural hearing loss or renal disease • *Epstein syndrome*: mild-to-moderate thrombocytopenia with cytoplasmic inclusions (Dohle bodies) in peripheral blood leukocytes, however leukocyte inclusions are structurally different from May Hegglin anomaly **Bernard-Soulier syndrome** • Autosomal recessive • Decreased or absent expression of von Willebrand factor (vWF) receptor on platelets (GP1b) • Bleeding can be mild to severe, degree of thrombocytopenia also varies **DiGeorge syndrome** • 22q11.2 deletion • Cardiac anomalies, hypoplastic thymus, hypocalcemia • Mild thrombocytopenia with variable bleeding; usually mild **Paris-Trousseau syndrome** • Terminal deletion of the long arm of chromosome 11 • Associated with 90% of cases of Jacobson syndrome • Mild-to-moderate thrombocytopenia; however, platelet count can be normal • Variable bleeding diatheses due to abnormal response to thrombin and fused α granules

Continued

TABLE 1. (Continued)

SIZE	
	Gray platelet syndrome • Autosomal recessive/autosomal dominant; chromosome 3p21 involving *NBEAL2* • Lack of α granules • Bleeding is mild to moderate **Type 2B von Willebrand disease (vWD)** • Autosomal dominant • Moderate-to-severe bleeding • "Gain-of-function" mutation in vWF (vWF binds more readily to platelet receptor GP1b) **Platelet-type vWD** • Phenotypically similar to type 2B vWD; however, the gain-of-function mutation is in the GP1b on platelets, not the vWF **Hermansky-Pudlak** • Autosomal recessive • Oculocutaneous albinism, pulmonary fibrosis, inflammatory bowl disease (subtype specific) • Bleeding due to platelet storage defect (lack of dense granules) **X-linked thrombocytopenia with associated dyserythropoiesis or thalassemia** • *GATA1* mutation; X-linked • Large or normal-sized platelets • Severe thrombocytopenia with anemia • Bone marrow shows erythroid dysmorphology, mild anemia, and hypercellular marrow

systemic manifestations, including skeletal abnormalities, eczema, hearing loss, and developmental delay. In general, if the thrombocytopenia results from abnormal megakaryocytopoiesis, it is usually present at birth or develops in early infancy. Although bleeding can be severe in neonates with inherited platelet disorders, congenital platelet disorders are usually associated with a wide range of bleeding symptoms. For example, Glanzmann thrombasthenia (GT) leads to platelet dysfunction because of a decrease or absence of the fibrinogen receptor GPIIb/IIIa on the platelet surface. Infants affected with GT lack fibrinogen bridging of platelets to other platelets, and therefore, the platelet plug fails to form. In this disease, the platelet count is not always severely low, but any assay that assesses platelet function will be abnormal. Neonates with GT can have ICHs, gastrointestinal bleeding, and skin hemorrhages. Conversely, Bernard-Soulier syndrome is caused by an absence of the glycoprotein 1b receptor, which is responsible for platelet adhesion to vWF. Neonates affected with Bernard-Soulier syndrome also have mild thrombocytopenia, large platelets detected on blood smear, and lack of aggregation solely to ristocitin (as seen on platelet aggregation assay).

There is no specific therapy for the vast majority of inherited platelet disorders. For the most part, management of such cases usually consists of general measures aimed at avoiding bleeding; however, as the bleeding phenotype becomes more severe, therapy can be tailored. Affected patients can have platelet counts that fluctuate and at times, spontaneously improve. When bleeding does occur, platelet transfusions may be required. Recombinant factor VII can also be used to treat severe bleeding as a means to limit exposure to donor platelets and prevent platelet refractoriness from sensitization. The hospital blood bank should use blood products aimed at limiting the number of donor exposures (ie, single-donor transfusions).

Transient Abnormal Myelopoiesis

Transient abnormal myelopoiesis (TAM) is a myeloproliferative syndrome that is unique to fetuses and neonates with trisomy 21 syndrome. Although the fetal presentation is associated with a high mortality rate if the presentation occurs postnatally, TAM usually resolves by age 6 months. However, despite resolution, 20% to 30% of infants subsequently develop acute myeloid leukemia, which is clonally similar to TAM. Approximately 20% to 30% of infants with TAM have an associated leukocytosis but 40% present with thrombocytopenia, which can be isolated. Therefore, infants with trisomy 21 who have isolated thrombocytopenia of unknown etiology should be evaluated by a pediatric oncologist and/or undergo flow analysis of peripheral blood to assess for blasts. (14)

HEMOPHILIA AND RARE FACTOR DEFICIENCIES

Generation of thrombin is the central event in the blood coagulation process, and thrombin is essential to achieve hemostasis. Hemophilia is associated with absence or reduced production of thrombin as a result of a deficiency of coagulation factors. This disorder has an X-linked recessive inheritance pattern and affects male patients almost exclusively, except in the case of female lyonization. Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are the most common types of hemophilia, affecting 1 in 5,000 and 1 in 25,000 male patients of all racial groups, respectively. Factor deficiency is categorized by the degree of plasma factor activity (<1% = severe; 1%–5% = moderate; >5%–40% = mild), which correlates indirectly with the disease severity. At birth, neonatal levels of factor VIII are at adult levels, allowing for easy identification of factor VIII deficiency in the newborn period. In contrast, newborns have approximately 50% of adult levels of factor IX, making the diagnosis of milder forms of factor IX deficiency more difficult in the newborn period. Patients with hemophilia have a prolonged aPTT level that corrects after mixing studies. To confirm the diagnosis, specific laboratory assays can be performed to detect low factor VIII and IX levels. It is important to note that type 3 von Willebrand disease is clinically similar to severe hemophilia A, with low factor VIII levels and a prolonged aPTT. Therefore, a vWF assay should be performed on all infants with low factor VIII levels, regardless of the level of deficiency, because the result of this will influence the type of factor product used for treatment.

Seventy-five percent of infants with severe hemophilia are diagnosed by 1 month of age. (15) In the neonate, common sites of bleeding are extracranial sites (eg, cephalohematoma) and sites of medical procedures (eg, heelstick, circumcision, venipuncture, or scalp monitor). Although an uncommon complication, ICH can occur in 3% to 7% of neonates with severe hemophilia. (15) Risk factors for spontaneous ICH include severity of factor deficiency, nulliparity, prolonged second stage of labor, and use of forceps or vacuum devices for assisted delivery. Providers should obtain a head ultrasound scan in a neonate with moderate or severe hemophilia before discharge from the hospital.

Once the diagnosis of hemophilia is confirmed, the management approach should be determined in consultation with a pediatric hematologist. Education of the family should begin immediately, and arrangements should be made to deliver factor product to the home before discharge. A complication of hemophilia treatment is the development of an inhibitor, which usually occurs shortly after replacement therapy has been initiated. Rate of inhibitor development is 30% in patients with hemophilia A and about 5% in patients with hemophilia B. Suggested risk factors include type of replacement factor product (recombinant vs plasma-derived) and age at the time of initial replacement. It is imperative to treat affected patients with the safest form of factor available after extensive discussion with the family about inhibitor development. With guidance from a hematologist, dosing of the factor product is based on the volume of distribution, half-life of the specific factor product, and severity of bleeding.

Rare factor deficiencies have an autosomal recessive pattern of inheritance and have a prevalence of 0.5 to 2 per 1 million in the population. Factor XIII is known as the “fibrin stabilizing factor” and is responsible for clot stability. Symptoms of factor XIII deficiency are usually found in patients with activity levels less than 5%, with bleeding from the umbilical stump occurring in about 80% of cases. The incidence of ICH in neonates with factor XIII deficiency is approximately 25% to 30%, which is much higher than that seen in hemophilia A and B. Other symptoms include poor wound healing and delayed postoperative bleeding; maternal family history may include recurrent spontaneous miscarriages. Management of factor XIII deficiency in neonates includes monthly infusions of recombinant or plasma-derived factor products, but cryoprecipitate can also be used if factor product is not available.

Neonates with factor XII deficiency will have a prolonged in vitro aPTT but lack clinical symptoms.

Factor XI deficiency affects both men and women and results in a bleeding disorder of variable severity, without correlation to plasma level. It can be inherited in a homozygote, compound heterozygote, or autosomal dominant pattern, depending on the mutation. (16) Congenital factor XI deficiency is common amongst Ashkenazi Jews with a rate of heterozygosity as high as 8% to 9%. (17) At present, factor XI concentrates are not available in the United States (they are only available in the United Kingdom and France on a limited basis), so if affected patients exhibit bleeding, replacement with fresh frozen plasma (FFP) is needed.

Severe factor II deficiency (aprothrombinemia) is incompatible with life.

VITAMIN K–DEPENDENT BLEEDING

Vitamin K is essential for the production and function of procoagulant factors II, VII, IX, and X and naturally occurring anticoagulants protein C and S. Deficiency of vitamin K is common in newborns, and without replacement, these infants are at risk for vitamin K–dependent bleeding (VKDB). VKDB can be classified according to the time of onset—early, classic, and late (Table 2). Early-onset VKDB occurs by the first day after birth and is found in infants born to women receiving medication that interferes with vitamin D activity (eg, anticonvulsants, antibiotics, and vitamin K antagonists). Classic VKDB results from physiologic deficiency of vitamin K at birth, compounded by a lack of vitamin K in breast milk or inadequate feeding. Late-onset VKDB can present within the first and 12th weeks of age but most commonly between the third and eighth weeks of age. (18) This form is found exclusively in breastfed infants or in children who are unable to absorb vitamin K.

Clinical manifestations of VKDB include bruising, gastrointestinal bleeding, and ICH. The laboratory abnormalities associated with vitamin K include prolonged PT and an increased international normalized ratio (INR), with normal levels of D-dimer, fibrinogen, and platelet count. A prolonged PT is the only laboratory finding in patients with mild vitamin K deficiency. However, if the vitamin K deficiency is severe, both the PT and aPTT can be prolonged. Additional testing is rarely needed to confirm the diagnosis. However, if confirmation is required, testing can include direct measurement of vitamin K levels or documentation of elevated levels of noncarboxylated prothrombin using the protein-induced vitamin K absence assay. All infants with VKDB should be given 0.5 to 1 mg of subcutaneous or intravenous vitamin K. The INR has been shown to be corrected to 30% to 50% of normal as quickly as 1 hour after intravenous administration, with the bleeding reduced as soon as 20 minutes. (19) For severe bleeding, it may be necessary to administer blood products such as FFP or factor replacement with recombinant factor VII until the PT/INR normalize. (20)(21)

The World Health Organization recommends that all newborns receive 1 mg of vitamin K intramuscularly after birth. In the era of prophylaxis, VKDB has become rare. However, recent literature reports a rise in late-onset VKDB because of omission or refusal of prophylaxis at birth. (22) Without intramuscular vitamin K prophylaxis, the incidence of late VKDB increases from 0.24 to 3.2 cases per 100,000 live births (22) to 4.4 to 7.2 per 100,000 live births. (23) Late-onset VKDB is associated with significant morbidity, with 50% to 80% of patients presenting with an ICH. (24)(25) In a retrospective study of 11 cases of ICH associated with late VKDB, 8 patients (72%) had significant morbidity, including cerebral palsy, seizures, and severe psychomotor retardation. (26)

BLEEDING DISORDERS IN SICK INFANTS

Disseminated Intravascular Coagulation

DIC is an acquired syndrome characterized by a massive inflammatory response with endothelial damage and systemic activation of the coagulation system. It causes both hemorrhage and microvascular thrombosis. DIC in neonates can be attributable to several underlying conditions, such as sepsis, severe asphyxia, necrotizing enterocolitis, liver dysfunction, and vascular tumors. (27) Laboratory findings include prolongation of the PT/aPTT, low fibrinogen, elevated D-dimers, and hemolytic anemia.

Liver Disease

The liver is responsible for the synthesis of most pro- and anticoagulant proteins as well as thrombopoietin. Neonates with liver failure may present with both bleeding and thromboses. Overwhelming hepatic dysfunction presents similar to DIC. The PT, expressed as INR, is used as an indicator of the severity of liver damage and helps determine transplant eligibility. In patients with bleeding as a result of liver failure, management is supportive while attempts are made to identify the underlying primary disease.

Management of DIC and Liver Failure

If a neonate has DIC or liver failure, FFP will replace all coagulation proteins. However, large volumes are required, which may lead to complications, particularly in patients who are already fluid overloaded. (28) Off-label use of recombinant factor VIIa has been used in affected patients and has been shown to control bleeding from liver disease and DIC in neonates and children; however, this

TABLE 2. **Vitamin K Deficiency Syndromes**[a]

TYPE	TIME OF ONSET	CAUSE
Early	First 24 hours after birth	Maternal anticonvulsants, antibiotics
Classic	1 to 7 days after birth	Poor vitamin K intake, usually in breastfed infants
Late	1 to 8 weeks after birth	Fat malabsorption (eg, biliary atresia, cystic fibrosis, α_1-antitrypsin deficiency); rarely, antibiotics or poor intake

[a] *Reprinted with permission from Manco-Johnson MJ. Bleeding Disorders in the Neonate.* NeoReviews. *2008;9(4):e166*

medication increases the risk of thromboses. (29)(30)(31) Cryoprecipitate can be used to correct the low fibrinogen found in these patients but this product does not contain other vitamin K–dependent factor products.

CONCLUSION

Coagulation disorders are encountered relatively frequently in the NICU. Knowledge of the various abnormalities that are commonly seen as well as a logical approach to the diagnosis and management of the bleeding neonate will lead to improved outcomes.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and pathophysiology of neonatal thrombocytopenia and thrombocytosis.
- Know the clinical and laboratory manifestations and management of neonatal thrombocytopenia and thrombocytosis.
- Know the inheritance patterns of the common factor deficiencies.
- Know the causes and pathophysiology of acquired defects in hemostasis.
- Know the causes and pathophysiology of congenital defects in hemostasis.
- Know the clinical manifestations, laboratory findings, and management of congenital defects in hemostasis.

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1. A primigravida delivers her infant at term gestation. The infant is noted to have some petechiae and has a complete blood cell count measurement. The platelet count is $10\times 10^3/\mu L$ ($10\times 10^9/L$). Repeat testing confirms this result. The maternal platelet count is normal. Which of the following is the most appropriate management course for this infant?
   - A. Any therapeutic actions should be withheld until confirmatory testing of the father and mother are established.
   - B. The father should be asked to provide a directed platelet donation to the infant if it is fairly certain that he is indeed the biological father.
   - C. Although the platelet count from the laboratory is abnormal, the likelihood of any clinical consequence is so low that platelet transfusion is contraindicated.
   - D. The recurrence risk will be low during subsequent pregnancies, and have less severe findings if the low platelet count does recur.
   - E. Along with platelet transfusion, administration of intravenous immunoglobulin can increase the infant's platelet count and also protect the transfused platelets from antibodies.
2. A newborn infant has thrombocytopenia. Upon further investigation, it is noted that the mother has systemic lupus erythematosus and associated thrombocytopenia. Which of the following statements regarding this infant's condition is correct?
   - A. The expected course will be persistent thrombocytopenia for the first 6 months.
   - B. The risk of intracranial hemorrhage is less than 1%.
   - C. Steroids are contraindicated for this condition because they may cause platelet dysfunction.
   - D. This condition is most likely due to paternal antibodies to maternal antigens.
   - E. This infant is very likely to have stunted growth and severe developmental delay.
3. A term male infant has persistent oozing from his circumcision site. Factor VIII levels are less than 1%. He is treated with a factor VIII concentrate, which helps initially, but he starts bleeding again within a few hours. What other coagulation assay should be performed to further elucidate his diagnosis?
   - A. Thrombin time.
   - B. Complete factor assay including factors I through XII.
   - C. von Willebrand factor assay.
   - D. Factor XIII assay.
   - E. Follow complete blood cell count every hour for 6 hours.
4. A patient with a history of early death in a sibling and a family history of bleeding disorders undergoes a laboratory evaluation. Test results are normal except for an isolated prolongation of prothrombin time. There are no clinical symptoms. Deficiency of which coagulation factor is responsible for isolated prolonged prothrombin time?
   - A. Factor VII.
   - B. Factor VIII.
   - C. Fibrinogen
   - D. Factor V.
   - E. Factor XII.

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5. A family refuses vitamin K for their newborn infant without any good reasons to support this request. Which of the following statements regarding vitamin K and bleeding in the newborn period is correct?
    - A. Vitamin K deficiency is fairly common, with vitamin K–dependent bleeding occurring in 10 to 15 per 10,000 live births when prophylaxis is not provided.
    - B. Although intracranial hemorrhage can occur with vitamin K deficiency, no cases of long-term complications, such as cerebral palsy or seizures, have been described.
    - C. Late-onset vitamin K–dependent bleeding, which occurs in exclusively breastfed infants, can present within the first and 12th weeks of age, but most commonly between weeks 3 and 8.
    - D. Affected patients will have normal prothrombin time, thrombocytopenia, and low fibrinogen and D-dimer levels.
    - E. The appropriate treatment for gastrointestinal bleeding is 1 mg of oral vitamin K.

Coagulation Disorders in the Newborn

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Neonatal Neutropenia

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Education Gap

Most cases of neonatal neutropenia are self-limited. However, because neutrophil function is a crucial component of innate immunity, neonatal neutropenia must be identified promptly and treated based on risk of clinical infection.

Abstract

Neonatal neutropenia is a common laboratory finding noted on the complete blood cell count of neonates in the intensive care unit. Neonatal neutropenia has various causes, ranging from maternal conditions to congenital syndromes to immune-mediated processes. However, not all neonatal neutropenia is clinically relevant; it often does not increase the risk of infection. In this review, we will discuss neutrophil function and development, review the causes of neonatal neutropenia, and describe their clinical relevance, evaluation, and management options.

Objectives After completing this article, readers should be able to:

1. Review normal development and function of neonatal neutrophils.
2. List primary causes of neutropenia based on categories of increased destruction and decreased production.
3. Review evaluation of neonatal neutropenia including clinical and laboratory findings.
4. Evaluate treatment options for severe, persistent neutropenia.

CLINICAL CASE

JC is a female neonate born at 30 weeks' gestation with a birthweight of 1,400 g (43%). Her mother is a 40-year-old woman with a history of advanced maternal age and depression. She presented in preterm labor and received 1 dose of betamethasone before delivery. There were no concerns for infection. JC required continuous positive airway pressure. At 3 days of age, JC was noted to have an absolute neutrophil count of 196/μL (196×10^9/L), which was confirmed with repeat testing. The neonatologist discusses this case with the pediatric residents and neonatology fellow and asks them to research the clinical significance of this finding and the most appropriate management.

AUTHOR DISCLOSURE Drs Moerdler and LaTuga have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ANC	absolute neutrophil count
CBC	complete blood cell count
ELBW	extremely low birthweight
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HNA	human neutrophil antigen
IgG	immunoglobulin G
IUGR	intrauterine growth restriction
IVIG	intravenous immunoglobulin
PIH	pregnancy-induced hypertension
SCN	severe congenital neutropenia
SGA	small for gestational age
VLBW	very low birthweight

BACKGROUND

When reviewing results of a complete blood cell count (CBC), providers typically focus on values outside the normal range. In pediatric populations, normal ranges vary based solely on age. In contrast, normal neutrophil counts in premature neonates vary by gestational age at birth and birthweight. Low neutrophil counts are quite common in the neonatal period; an absolute neutrophil count (ANC) less than 1,000/μL ($1{,}000 \times 10^9$/L) has been reported in about 8% of all NICU admissions. With approximately 400,000 NICU admissions in the United States annually, there are about 32,000 cases of neutropenia each year.

Are all cases of neonatal neutropenia clinically relevant? Why are neutrophils crucial for neonatal immune function? What is the best management approach to neonatal neutropenia? Among neonates with congenital bone marrow syndromes such as Kostmann syndrome and chemotherapy-induced neutropenia, neutropenia has been related to higher rates of infection. However, most cases of neonatal neutropenia do not carry an increased risk of sepsis and mortality. In this review, we will discuss neutrophil development and function, define neutropenia in relation to reference ranges, review causes of neonatal neutropenia, and provide a framework for the evaluation and management of neutropenia.

NEUTROPHIL DEVELOPMENT AND FUNCTION

Bone marrow hematopoiesis begins around 22 weeks of gestation, but full neutrophil production (levels in the normal range) does not begin until the third trimester. Therefore, the lower the gestational age at birth, the less time for neutrophil development and production, resulting in a more immature neutrophil pool. Furthermore, preterm neonates have not had sufficient time to be exposed to pathogens and develop an adaptive response. Because of their lack of a functional adaptive immune system, preterm infants rely solely on the innate immune response. Neutrophils are the infantry in the first line of defense in innate immunity; they consume and destroy foreign organisms. Therefore, neutropenia can increase the risk of bacterial infections.

Neonates have both quantitative and qualitative neutrophil deficits that render them different from children and adults. To start, neutrophil kinetics in neonates are dynamic, with dramatic peaks and troughs within the first few days after birth. In addition, neonates have a smaller neutrophil reservoir from which to respond to infections. The neonatal storage pool is twice the size of circulating neutrophil amounts compared with the adult pool, which is about 10 times the size of circulating levels. As a result, during infection, adults usually develop neutrophilia from the acceleration of neutrophil production in marrow, engagement of progenitors into production, and release of neutrophils from storage into circulation. In comparison, during a time of infection, neonates deplete their neutrophil reserves quickly without time to accelerate progenitor granulocyte maturation and production. Furthermore, when infants need to activate a neutrophil response, they have less ability to mobilize the mature cells from their storage pools. In theory, these differences are due to decreased production of myeloid growth factors in utero. At birth, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) levels are high in the umbilical cord blood, suggesting that myelopoiesis is already running at its maximum rate. Therefore, neonates cannot further boost or accelerate myelopoiesis in the setting of stress or infection.

Functionally, neonatal neutrophils are less effective than those of older children and adults. Because neutrophils are being produced quickly, it is believed that cells might have less time for key differentiation steps during maturation, which leads neutrophils to be deficient in cytotoxic granules compared with those in adults. Neutrophil function in neonates also differs from that in adults in areas such as adhesion, chemotaxis, release of neutrophil extracellular traps (called NETosis, which leads to cell death), and phagocytosis. These differences result from enzyme deficiencies and protein activity affecting respiratory burst and ultimately clearance of pathogens (Fig). Despite these differences and deficiencies, neutrophil function usually improves around 2 to 3 weeks of age and continues to gradually increase.

DEFINITION OF NEUTROPENIA

The ANC is calculated by multiplying the white blood cell count by the sum of the percentages of segmented neutrophils and bands seen on peripheral blood smear. Neutropenia is not as clearly defined. Statistically, neutropenia is defined as an ANC greater than 2 standard deviations below the mean or below the fifth percentile for age. Because of the differences in neutrophil kinetics, adult normal ranges are not accurate for neonates. Most recently, Schmutz et al (1) reviewed normal neutrophil ranges in a large cohort of neonates with gestational ages ranging from 23 to 42 weeks while accounting for sex, altitude, and labor history. Overall, neutrophil counts of neonates change on a scale of hours within the first 2 to 3 days, with a peak between 12 and 24 hours after birth, followed by a gradual decline by 2 to 3 days. Despite the fact that rudimentary cutoffs do not reflect the

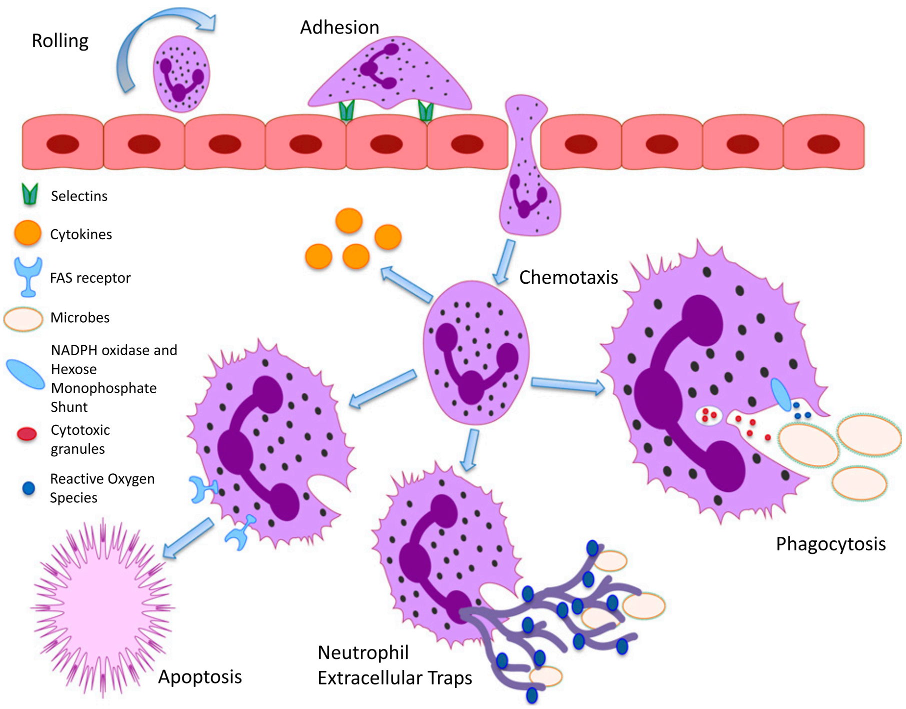

Figure. Normal neutrophil functions. Neutrophils circulate in the bloodstream and are recruited to sites of infection by including mechanisms such as selectins, which are upregulated in response to inflammation and assist in adhesion to the endothelium. After adhering to the endothelium, neutrophils can marginate to the site of infection where they get activated. Activated neutrophils have various mechanisms of action: engulfment and killing of microbes using cytotoxic enzymes contained in their granules, including lactoferrin and myeloperoxidase proteins; generation of reactive oxygen species by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the hexomonophosphate shunt; release of neutrophil extracellular traps; and cytokine production to stimulate an inflammatory response. After killing the microbe, neutrophils self-regulate with cell death via mechanisms such as the Fas receptor binding. Neonatal neutrophils have deficiencies at nearly each step of normal neutrophil function.

statistical extremes of neonatal neutropenia, clinicians continue to rely on ANC of less than 1,500/μL (1.5×10^9/L) for mild and ANC of less than 500/μL (0.5×10^9/L) for severe neonatal neutropenia.

INCIDENCE OF NEUTROPENIA

Neutropenia is relatively common among neonates. The incidence varies by ethnicity, gestational age, and growth patterns. More than 10% of neonates of black, African, and Arabic descent demonstrate an ANC less than 1,500/μL (1.5×10^9/L). It is more common in infants born prematurely (<36 weeks' gestation) and inversely proportional to birthweight. Other associated risk factors include female sex, high-altitude delivery, and mode of delivery. Exposure to labor and vaginal delivery have been associated with improved neutrophil function, possibly because of immune priming.

CAUSES OF NEUTROPENIA

The primary causes of neonatal neutropenia can be divided into broad categories of decreased production, increased destruction, and a surge in margination of neutrophils (**Table**).

Decreased Neutrophil Production

In premature infants, early-onset neutropenia has been correlated with sepsis, maternal hypertension, intrauterine growth restriction (IUGR), small for gestational age (SGA), asphyxia, and periventricular hemorrhage. Although sepsis has been described as a reason for neutropenia, it is not clear if it is the inciting event or a consequence of neutropenia. Sepsis leads to increased demand for neutrophils in peripheral tissues or at the sight of the infection, and therefore depletes the bone marrow of its neutrophil reserves. Neutropenia induced by an underlying bacterial infection or sepsis is usually transient, and in the setting of a critically ill neonate with organ dysfunction, the neutropenia can be a marker of overwhelming sepsis with associated bone marrow suppression.

Late-onset neutropenia, also known as *idiopathic neutropenia of prematurity*, is often seen in neonates with associated anemia and reticulocytosis. It usually occurs between 6 and 8 weeks of age, but in very low-birthweight (VLBW) infants, late-onset

TABLE. **Causes of Neonatal Neutropenia**

DIMINISHED NEUTROPHIL PRODUCTION
Maternal and pre-natal conditions – maternal hypertension, pre-eclampsia, pregnancy-induced hypertension, intrauterine growth restriction
Twin-twin transfusion
Rh hemolytic disease
Congenital bone marrow failure syndromes (Kostmann syndrome, cyclic neutropenia, reticular dysgenesis, Barth syndrome, Shwachman-Diamond syndrome, cartilage-hair hypoplasia)
Inborn errors of metabolism (organic acidemias, glycogen storage disease type 1b)
Viral infections (parvovirus, cytomegalovirus, rubella)
Copper deficiency
Alloimmune neutropenia with anti-NB1 antibodies
ACCELERATED NEUTROPHIL DESTRUCTION (OR UTILIZATION)
Bacterial or fungal sepsis (including necrotizing enterocolitis)
Immune-mediated (alloimmune neutropenia of the newborn, autoimmune neutropenia of infancy, and isoimmune or neonatal autoimmune neutropenia)
EXCESSIVE NEUTROPHIL MARGINATION
Drug-induced
Idiopathic neutropenia of prematurity
Necrotizing enterocolitis

neutropenia can be observed as early as 3 weeks of age with a median age of 6 to 8 weeks. Based on recent data from Vetter-Laracy et al, (2) late-onset neutropenia with ANC less than $1,500/\mu L$ ($1.5 \times 10^9/L$) has been found in up to 20% to 65% of VLBW neonates and up to 74.3% of extremely low-birthweight (ELBW) neonates. Late-onset neutropenia may be the result of bone marrow progenitors competing for production of red blood cells versus white blood cell, possibly because of an imbalance of erythropoietin and G-CSF. Although it is relatively common among VLBW and ELBW infants, late-onset neutropenia resolves spontaneously and does not correlate with sepsis.

Maternal hypertension, preeclampsia, and pregnancy-induced hypertension (PIH) are common problems that can lead to early-onset neonatal neutropenia. The incidence of this type of neutropenia can be as high as 49% among growth-restricted infants, especially among neonates born to mothers with PIH. The severity of the neutropenia is proportional to the degree of growth restriction. Although the causes are unclear, restriction of placental blood flow may lead to decreased production of growth factors, including myeloid colony-stimulating activity, decreased progenitor responsiveness to growth factors, decreased neonatal bone marrow production, and decreased neutrophil storage pools. Alternatively, it may be due to placental production of an inhibitor of myelopoiesis. Other data suggest that high levels of erythropoietin force early progenitors to erythrocyte production, leaving fewer progenitors to differentiate along the myeloid cell path. Clinically, PIH-associated neutropenia presents within the first week after birth with an ANC as low as less than $500/\mu L$ ($0.5 \times 10^9/L$). It resolves quickly and spontaneously, usually within 2 to 3 days. The speedy resolution of PIH-associated neutropenia suggests that it is unlikely to increase the risk of bacterial sepsis.

Neonatal neutropenia has many congenital causes, many of which present early in the first year of age and are associated with recurrent fevers and severe infections. Though the overall incidence of congenital neutropenia is unknown, some studies suggest that about 2 million children have congenital neutropenia. In cyclic neutropenia, the neutropenia presents at regular intervals, usually every 21 days with predictable fluctuations in neutrophil and monocyte counts. The most common mutations associated with congenital neutropenia are ELANE, HAX-1, and G6PC3. Both cyclic neutropenia and severe congenital neutropenia (SCN) are usually caused by ELANE, which is only expressed in myeloid tissues and therefore, causes no extramedullary manifestations.

Kostmann syndrome is a severe form of SCN caused by an absence of myeloid progenitors or “maturation arrest” at the promyelocyte-myelocyte stage, leading to increased apoptosis of precursors. Some patients with Kostmann syndrome also have mutations and abnormalities of the G-CSF receptor. X-linked neutropenia, another form of SCN, results from a mutation in the Wiskott-Aldrich syndrome protein and is associated with thrombocytopenia and neutropenia, which can transform into myelodysplastic syndrome.

Shwachman-Diamond syndrome results from ribosomal dysgenesis and consists of neutropenia, exocrine pancreatic insufficiency, skeletal abnormalities, and failure to thrive. Barth syndrome is a rare X-linked disorder caused by a defect in phospholipid metabolism, which presents with cardiomyopathy, organic aciduria, motor and growth delays, and neutropenia. Reticular dysgenesis is caused by a mitochondrial gene mutation that results in a subsequent defect in hematopoietic stem cell development. Clinical presentation includes severe neutropenia, lymphoid dysplasia, and agammaglobulinemia.

Cartilage-hair hypoplasia arises from a defect in mitochondrial RNA processing, leading to dwarfism and decreased neutrophil precursors. In addition, inherited disorders of metabolism including organic acidemias such as methylmalonic acidemia, may have associated neutropenia and present in the first week after birth. In glycogen storage type 1b, neonates present with hypoglycemia, hepatomegaly, enterocolitis, and neutropenia because of increased neutrophil apoptosis.

Other causes of neutropenia include twin-twin transfusion, which leads to decreased neutrophil production in the "donor" twin. In Rh hemolytic disease, progenitor cells are driven toward erythrocyte lineage and development to increase red blood cell production at the cost of myeloid development. Copper deficiency is another known cause of neutropenia, though the mechanism is not understood. Neutropenia has been found in neonates with hypoxic-ischemic encephalopathy and periventricular hemorrhage. Certain medications have also been associated with neutropenia including β-lactam antibiotics, thiazides, ranitidine, and acyclovir.

Increased Neutrophil Destruction

Immune-mediated neutropenia is the major cause of neutrophil destruction leading to neonatal neutropenia. Three types of immune etiologies exist: alloimmune neutropenia of the newborn, autoimmune neutropenia of infancy, and isoimmune or neonatal autoimmune neutropenia. In alloimmune neutropenia, there is an incompatibility of paternal antigens on the fetal neutrophils which are recognized by maternal antibodies. After an initial immunizing event, maternal immunoglobulin G (IgG) alloantibodies are transferred transplacentally to the fetus, where they recognize the paternal human neutrophil antigen (HNA) expressed on the fetal neutrophil, leading to engulfment and destruction by splenic macrophages. This process is similar to hemolytic disease of the newborn but with destruction of neutrophils as opposed to erythrocytes. The degree of neutropenia is affected by the antibody titer level as well as the IgG subclass of the antibody. The most common alleles in the United States include HNA1a, -1b, -1c, which are polymorphisms of *FCGR3B*. Up to 20% of pregnant women carry circulating antineutrophil antibodies, but fewer than 1% of neonates develop alloimmune neutropenia. Clinical symptoms develop within the first 2 weeks after birth and may include delayed umbilical cord separation, severe omphalitis, cellulitis/skin infections, bacterial infections, and meningitis. Many of these symptoms are severe, with a 5% mortality rate. Alloimmune neutropenia of the newborn is self-limiting with antibody clearance usually occurring within 6 weeks of age, with a median neutropenia period of 7 weeks. In rare cases, neutropenia can last up to 6 months.

Another type of immune-mediated neutropenia is autoimmune neutropenia *of infancy*, which is similar to autoimmune hemolytic anemia or autoimmune thrombocytopenia. Although the underlying etiology of antibody development is unknown, some suggest associations with parvovirus B19 infection or β-lactam antibiotics. The antibodies found in this disorder can be the same type as in the other immune-mediated neutropenias, however they are not maternal antibodies. Instead, these are neonatal-produced antibodies. In addition to decreasing the ANC, these antibodies can have an independent impact on innate immunity, including neutrophil function, mobility, and adhesion. Autoimmune neutropenia of infancy is more commonly seen in infants and young children aged 3 to 30 months old as opposed to neonates, though neonatal cases have been reported. Similar to the other immune-mediated causes of neutropenia, clinical symptoms are usually mild and include otitis media, skin, respiratory, and gastrointestinal infections, though infants can occasionally develop more severe infections and sepsis.

The third type of immune-mediated neutropenia is isoimmune or neonatal autoimmune neutropenia. These cases are caused by passive transplacental transfer of maternal IgG antibodies from mothers with a history of autoimmune neutropenia or who are Fcγ RcRIIIb deficient. In these cases, usually both the mother and infant are neutropenic. The neutropenia is transient, because it resolves with clearance of the autoantibodies. Infants usually remain asymptomatic.

EVALUATION OF NEUTROPENIA

From the CBC and its differential count, calculation of the immature to total neutrophil ratio can help to differentiate between neutropenia of decreased production from destructive or overutilization versus depletion of storage pools. The immature to total neutrophil ratio is calculated using the following formula:

$$(\text{Bands} + \text{Metamyelocytes} + \text{Myelocytes})/$$
$$(\text{Segmented neutrophils} + \text{Bands} + \text{Metamyelocytes} + \text{Myelocytes})$$

The accepted normal range of the immature to total neutrophil ratio in infants is from 0.05 to 0.27. Neutropenia with a normal immature to total neutrophil ratio suggests a problem with neutrophil production, such as IUGR/SGA and PIH-associated neutropenia. However, an immature to total neutrophil ratio greater than 0.3 is considered to be elevated, suggesting a "left shift" with increased immature neutrophils circulating in the periphery due to peripheral destruction or increased margination from the bone marrow storage pools. This can be found in the setting of sepsis or immune-mediated destruction such as alloimmune neutropenia.

When faced with a neonate with neutropenia, it can be helpful to remember the more common causes of neutropenia in infants in the NICU, such as sepsis, IUGR/SGA, and PIH. As discussed before, these causes of neutropenia are usually transient and the neutropenia will resolve spontaneously or with treatment of the underlying infection. In the case of a neonate with sepsis, most experts recommend a repeat CBC. If the neutropenia resolves within 2 to 3 days, no further testing is needed. However, if the neutropenia persists, further evaluation is warranted. Similarly, for neonates born to mothers with maternal hypertension or with a history of IUGR/SGA, neutropenia that persists beyond 5 days needs further evaluation. However, because the risk of infection is directly related to length and severity of neutropenia, any neutropenia that lasts more than 5 days or has an ANC less than 500/μL (0.50×10^9/L) warrants a diagnostic evaluation.

Immune-mediated neutropenia is diagnosed by the demonstration of antibodies bound to the neutrophil surface or by circulating antibodies in the serum. Currently, antibodies can be detected using the granulocyte agglutination test, granulocyte immunofluorescence test and monoclonal antibody immobilization or granulocyte antigens.

Bone marrow biopsy and evaluation is reserved for severe persistent neutropenia, unclear etiology, after antibody detection testing, neutropenia unresponsive to G-CSF treatment, or persistent neutropenia with other cytopenias. Marrow evaluation can demonstrate storage pool size and stage of neutrophil maturation. This information differentiates between a production defect and depletion of the storage pool in the setting of a destructive process. Although many of these types of neutropenia have nonspecific bone marrow findings, marrow evaluation may help identify SCN, with its characteristic "maturation arrest."

MANAGEMENT OF NEUTROPENIA

In theory, G-CSF should treat neutropenia and possibly prevent neonatal neutropenia. However, the data are unclear. Some studies demonstrated protection from early or late-onset infections, whereas others (including a Cochrane review) showed only a transient effect with no change in infection-free survival. G-CSF is recommended for neonates with a diagnosis of congenital neutropenia such as SCN to reduce inpatient hospitalizations, decrease antibiotic use, and improve survival. Most experts do not recommend its use in transient or self-limited neutropenia due to maternal chronic hypertension, PIH, IUGR/SGA, twin-twin transfusion, or Rh hemolytic disease because the neutropenia is likely to resolve spontaneously within a few days.

In cases of severe neutropenia with an ANC less than 500/μL (0.5×10^9/L) for 2 to 3 days, few would argue with the use of G-CSF. Recombinant G-CSF stimulates neutrophil production and release from the bone marrow, increases marrow reserve, and decreases apoptosis. G-CSF is especially active in immune-mediated neutropenia because it may be able to downregulate antigen expression, leading to some protection from circulating antibodies as well as improvement in neutrophil function, which is affected by the antibodies. Recombinant GM-CSF stimulates production of both granulocyte as well as macrophage colonies. G-CSF has better ability to yield a steady state of neutrophil circulation but GM-CSF can promote both neutrophil and macrophage maturation. There are few adverse effects associated with short-term use, though some describe irritability possibly due to bone pain, as extrapolated from studies in older children and adults. Longer use requires monitoring for leukemic transformation, development of antibodies, and osteoporosis. The typical dose of G-CSF is 5 to 10 μg/kg per day via intravenous or subcutaneous injection, with rapid improvement of the ANC expected within 24 to 48 hours.

Other strategies with inconsistent results include intravenous immunoglobulin (IVIG) and corticosteroids. IVIG can improve neutrophil release from marrow storage pools to increase the peripheral ANC as well as assist with infections. However, not all patients with neutropenia respond to IVIG, with reported response rates being less than 50%. Steroids have not been shown to be as effective, though some cases of autoimmune neutropenia have shown slightly better outcomes with steroid treatment. Though granulocyte transfusions may help in acute situations, the long-term benefit remains unclear.

CONCLUSION

After reading the literature, the pediatric residents and neonatology fellow met again with the neonatologist to discuss the case of the newborn with neutropenia (clinical case described before). During the following 3 days, the infant's ANC remained below 200/μL (0.2×10^9/L). She remained clinically stable without findings of infection and her blood culture was negative. Because there was no maternal PIH to explain the neutropenia and the neutropenia was severe, the hematology team was consulted. The team recommended that JC should be treated with G-CSF. The infant's ANC increased from 186/μL (0.18×10^9/L) to 483/μL (0.48×10^9/L), then to 984/μL (0.98×10^9/L) in the subsequent days. By the time she was discharged 4 weeks later, the ANC had been in the 1,600 to 3,000/μL (1.60–3.0×10^9/L) range for 3 weeks. Though there was no evidence of infection, the hematology team suspected that a maternal infection was the most likely diagnosis of exclusion for this infant's neutropenia.

As this case illustrates, neonatal neutropenia is common. Though it typically resolves without intervention, treatment should be considered for severe, persistent neutropenia with an ANC $<500/\mu L$ *(*$0.50\times10^9/L$*).*

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the role of neutrophils in host defense.
- Know the changes that occur in circulating concentrations of polymorphonuclear neutrophils immediately after birth, under normal conditions.
- Recognize the causes and consequences of alterations in number and distribution of neutrophils.

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Hematologic Changes in Newborns with Neonatal Encephalopathy

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Education Gaps

1. Serial routine complete blood cell counts with differential, platelet counts, and nucleated red blood cell counts can provide valuable information on the timing and duration of a hypoxic-ischemic insult resulting in neonatal encephalopathy.
2. Complete blood cell count parameters may help differentiate other causes of neonatal encephalopathy.

Abstract

Neonatal encephalopathy is a disorder frequently observed by clinicians caring for sick neonates. One of the causes of this disorder is intrapartum hypoxia-ischemia. Caregivers are frequently called on to determine the etiology of neonatal encephalopathy, manage the disorder, and estimate the timing of any associated brain injury. Components of a complete blood cell count may be useful in assessing infants with neonatal encephalopathy. In this review, we discuss the usefulness of these parameters.

Objectives After completing this article, readers should be able to:

1. Describe the hematologic changes found in newborns with neonatal encephalopathy.
2. Identify trends in nucleated red blood cell counts to differentiate an acute versus remote hypoxic-ischemic insult.
3. Describe changes in the platelet count, lymphocytes, and hematocrit count that are associated with neonatal encephalopathy.
4. Recognize false-positive leukocytosis in the context of neonatal encephalopathy.
5. Apply the results of the complete blood cell count to assist in identifying other possible causes of neonatal encephalopathy.

AUTHOR DISCLOSURE Drs Dina and Muraskas have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CBC	complete blood cell count
NE	neonatal encephalopathy
NRBC	nucleated red blood cell
WBC	white blood cell

INTRODUCTION

Neonatal encephalopathy (NE) refers to neurologic dysfunction in the earliest days after birth among infants of 35 weeks or greater gestation. (1) NE may be categorized in 3 stages, as described by Sarnat and Sarnat, (2) and occurs in approximately 3 per 1,000 live births in developed countries. (3) NE is a general description of a neurologic condition that can be attributable to different causes, including hypoxia-ischemia, inflammation, or genetics. (1) Although NE describes a clinical condition, the term *asphyxia* denotes laboratory evidence of impaired gas exchange in a newborn, leading to progressive hypoxia, hypercarbia, and acidosis. The severity of the asphyxia depends on the extent and duration of the interruption. (4) Asphyxia may occur during, after, or remote from delivery. Intrapartum hypoxic-ischemic encephalopathy is a type of NE in late preterm and term newborns. It is a major cause of neonatal morbidity and mortality worldwide (5) and accounts for fewer than 15% of cases of cerebral palsy. (6) One resource to help determine if an infant's NE is attributable to an intrapartum hypoxic-ischemic event is the report of the American College of Obstetricians and Gynecologists on neonatal encephalopathy and neurologic outcome. (1)

There is no single proven biomarker that is diagnostic of NE, that can time an insult, or that can predict short- or long-term outcomes. (7) Maternal history, umbilical cord gases, placental pathology, Apgar scores, newborn clinical findings, serial newborn physical examinations, measures of organ function, and postnatal neuroimaging are of use in determining the cause and timing of NE. Hypoxic-ischemic insults may have hematologic effects that can cause aberrations in several components of a complete blood cell count (CBC). Serial CBCs can provide valuable information to confirm or refute the finding that an acute intrapartum or partial prolonged hypoxic-ischemic event was sufficient to cause NE in late preterm and term newborns.

Table 1 lists several common patterns of hypoxic-ischemic injury. A sudden marked or catastrophic decrease in cerebral blood flow and/or oxygenation to the fetal brain produces a near total (profound) asphyxial pattern. In this scenario, pregnant women often initially present with reassuring fetal heart rate patterns that abruptly become more ominous (category III). (8) In term newborns, the metabolically active "deep" gray matter regions, including the basal ganglia, thalami, putamen, internal capsule, and hippocampus, are vulnerable to acute profound injury. Frequently, injury to these areas ultimately results in dyskinetic cerebral palsy (choreoathetosis) and occasionally spastic quadriplegia.

Another major type of intrauterine fetal neurologic injury is the partial prolonged pattern. This injury may either occur within hours before birth (intrapartum) or may be more remote in occurrence. Remote insults may have occurred when a pregnant woman presents with a nonreactive tracing upon admission, often with a history of decreased fetal movements. Infants who have had a preexisting remote injury with recovery may not be able to tolerate labor and may require resuscitation after birth. Intrapartum partial prolonged injury may be found in pregnant women who have an initial reassuring presentation followed by a deterioration in the fetal heart rate tracing. Frequently, this type of injury is associated with cord compression, oligohydramnios, and placental insufficiency. As a response to either type of partial prolonged injury (ie, intrapartum or remote), intracranial blood is shifted from the periventricular regions toward the cortex and subcortical white matter. Some infants may demonstrate patterns of both profound and partial prolonged insults. (9)(10) Table 2 provides a summary of the types of hypoxic-ischemic intrauterine injury.

TABLE 1. **Common Patterns of Neonatal Hypoxic-Ischemic Injury**

PATTERNS OF INTRAUTERINE INJURY	FREQUENT FINDINGS
Acute profound	Sudden marked decrease in cerebral blood flow or oxygenation Reassuring FHR patterns that abruptly become a category III tracing Placenta abruption, cord prolapse, uterine rupture
Intrapartum partial prolonged	Reassuring FHR patterns followed by category II tracing that can progress to category III tracing Cord compression, oligohydramnios, and placental insufficiency
Remote partial prolonged	Nonreassuring FHR patterns on presentation History of decreased fetal movements Remote cord accident, maternal trauma
Combination of partial prolonged and acute profound	Presence of preexisting injury Fetuses recover in utero but unable to handle rigors of labor with terminal near total collapse

This table summarizes the common patterns of neonatal hypoxic-ischemic injury and the potential FHR pattern and common causes. FHR=fetal heart rate.

TABLE 2. **Types of Hypoxic-Ischemic Intrauterine Injury**

VARIABLE	ACUTE PROFOUND ASPHYXIA	PARTIAL PROLONGED ASPHYXIA WITHIN HOURS OF BIRTH[a]
NRBC (cell count/100 WBCs)	0–5	>10
Absolute NRBC count (NRBCs per cubic millimeter)	0–1,000	>1,000
Platelets ($\times 10^9$/L or $10^3/\mu$L)	≥150	<100

This table shows the NRBC count, absolute NRBC count, and platelet values commonly found in different patterns of asphyxia. NRBC=nucleated red blood cell; WBC=white blood cell.

[a] *Assuming measurements are taken 24 to 72 hours after the insult.*

ROLE OF CBCs IN EVALUATING NE

As noted previously, no single proven biomarker can determine the cause of the NE, pinpoint the timing of an injurious event, or predict the long-term neurologic outcome. (11) A comprehensive evaluation of multiple factors is the best way to assess neonates with NE. (1)(6) In our experience, serial CBCs with differential, platelet counts, and nucleated red blood cells (NRBCs) are an important part of such an evaluation, particularly among infants with a partial prolonged injury. Interestingly, a large proportion of infants who have had an acute, profound insult during the 30 minutes to 1 hour before birth lack changes in their CBCs or manifest laboratory changes indicative of multiorgan dysfunction.

Nucleated Red Blood Cells

NRBCs are erythropoietic progenitor cells that still contain a nucleus. These cells have been identified by different names in the literature, including erythroblasts, normoblasts, and megaloblasts. Under normal circumstances, these cells lose their nuclei and are released into the bloodstream to become mature red blood cells. NRBCs are normally present solely in the fetal and neonatal circulation. They are typically reported in the differential of a CBC from a newborn as a number of NRBCs per 100 white blood cells (WBCs) because automated systems can "misinterpret" NRBCs as leukocytes (ie, both contain nuclei). A manual differential should correctly interpret which cells are NRBCs, with a normal value in newborns ranging between 0 and 5%. The total "corrected" WBC count may then be calculated using the following formula:

$$\text{Corrected WBC count} = \text{Observed WBC} \times 100/(100 + \%\text{NRBCs})$$

In this equation, the units are the number of WBCs per cubic millimeter of blood. The "absolute" NRBC count is probably a more accurate reflection of the response to an in utero stress such as hypoxia-ischemia or infection. The absolute NRBC count is calculated with the following formula:

$$\text{Absolute NRBC count} = \text{Observed WBC count} - \text{Corrected WBC count}$$

The absolute NRBC count is reported as the number of NRBCs per cubic millimeter of blood. A normal absolute NRBC value is 500 to 1,000 NRBCs per cubic millimeter of blood.

Abnormally high NRBCs are often present in newborns with chronic hypoxia, such as with severely growth-restricted newborns. NRBCs may also be elevated as a result of maternal diabetes, maternal smoking, or fetal anemia. Among infants with NE, some investigators have concluded that the presence of increased NRBCs suggests significant antenatal stress for at least 6 to 24 hours. (12) The most commonly accepted mechanism for this finding is that either significant hypoxemia or inflammation stimulates the release of erythropoietin and other hematopoietic cytokines over 24 to 48 hours. This leads to an increased production and premature release of NRBCs from either the bone marrow or extramedullary hematopoietic sites to maximize the oxygen-carrying capacity of the fetal blood. (12) Christensen et al described the emergence of the NRBC into the peripheral circulation following fetal hypoxia as a multistage process after the administration of a synthetic erythropoietin analog. (13) They concluded that if the NRBC count is elevated at birth, a hypoxemic process commenced at least 28 hours before the stimulus. (13) On the other hand, other investigators believe that NRBCs may initially be released after only 6 hours of significant hypoxic-ischemic compromise. (14) NRBC counts tend to be higher at birth with delayed clearance in newborns with stage III NE, consistent with significant duration of injury. (15)(16) A correlation exists between a low cord pH, high base deficit, low Apgar score, and elevated NRBC counts. (17) NRBC counts tend to peak approximately 48 to 72 hours after a hypoxic or inflammatory stimulus.

Hematocrit

It is known that chronic hypoxia can result in neonatal polycythemia. However, because there are multiple reasons for neonatal polycythemia and this test cannot quantify the degree or duration of the hypoxia, the usefulness of the hematocrit count as an adjunct marker for NE is limited. (18)

Significant anemia at birth can be defined as a hemoglobin concentration less than 10 g/dL (100 g/L) and a hematocrit less than 30%. Studies have demonstrated a direct correlation between the severity of anemia and adverse neonatal outcomes. A fetal-maternal hemorrhage greater than 25% of the fetal blood volume (typically ≥80 mL) may be severe enough to cause NE. (19)

Platelets

Neonatal thrombocytopenia is defined as a platelet count less than $150\times10^3/\mu L$ ($150\times10^9/L$). It can be caused by a decrease in platelet production or an increase in platelet consumption secondary to disseminated intravascular coagulopathy. Approximately 30% of encephalopathic newborns have thrombocytopenia during the first week after birth. (20) If the thrombocytopenia is associated with elevated NRBCs, this suggests the possibility of a chronic remote insult. Most newborns with hypoxic-ischemic encephalopathy have low platelet counts without evidence of a consumptive coagulopathy. This entity has been identified as "thrombocytopenia of perinatal asphyxia." The exact mechanism of this finding is unclear. Some authors have proposed an inverse relationship between red blood cells and platelet production with stimulation of erythropoietin leading to a decrease in the number of immature megakaryocytes and decreased thrombocytopoiesis. (21) In support of this theory, animal studies have shown a reduction in the count and size of megakaryocytes after a hypoxic insult. (22) Further studies have suggested that platelet progenitor cells are not directly affected by hypoxia but rather, other bone marrow accessory cells are damaged and impair the effect of cytokines on megakaryocytes during megakaryocytopoiesis. (23)(24)(25) Christensen et al demonstrated that newborns with perinatal asphyxia had a nadir platelet count at 3 days of age; this thrombocytopenia was found to be greater than $40\times10^3/\mu L$ ($40\times10^9/L$) with a mean platelet count of $75\times10^3/\mu L$ ($75\times10^9/L$). (21) Similarly, Naeye and Lin reported that the nadir platelet count occurred approximately 7 hours after a hypoxic-ischemic insult. (26) Thrombocytopenia in asphyxiated newborns rarely requires a platelet transfusion. Table 2 provides an estimate of the NRBC and platelet counts observed in different patterns of asphyxia. These values may vary significantly, and frequently the timing and duration of an insult are indeterminate.

Platelet activity and aggregation can be affected by therapeutic hypothermia. Randomized controlled trials have shown that thrombocytopenia has been reported more often in hypothermic versus normothermic newborns. (27) Hypothermia appears not to affect other components of the CBC.

Lymphocytes

Studies have demonstrated that lymphocyte counts in newborns are dependent on the duration of fetal bradycardia. Fetal bradycardia in excess of 25 minutes resulted in absolute lymphocyte counts that increased by more than 10,000/μL (10×10^9 L). (26)(28) This elevation is relatively transient, with rapid normalization occurring within 18 to 24 hours, limiting its use as a marker for asphyxia. The authors attributed this lymphocytosis to a stress response that may have originated in the thymus.

White Blood Cells

WBCs can be falsely elevated in newborns with NE. Frequently, an elevated WBC count at admission is corrected downward when NRBCs are elevated (often noted as a small subscript in the hospital laboratory records). In theory, epinephrine used for delivery room resuscitation can falsely elevate WBCs because of demargination. (29) Newborn WBCs as well as platelet counts can be decreased by maternal conditions such as preeclampsia and hemolysis, elevated liver enzymes, and low platelet count syndrome.

Another common cause of NE is infection/inflammation that is typically associated with chorioamnionitis or a fetal inflammatory response. The findings of a WBC count less than $5\times10^3/\mu L$ ($5\times10^9/L$), an absolute neutrophil count less than 1,500/μL, or a left shift (immature to total neutrophil ratio >0.2) on the initial CBC are commonly found in newborns with sepsis. (10)

CONCLUSION

In a newborn with NE, serial CBCs with differential, platelet counts, and NRBC counts can provide useful and meaningful information to the neonatologist and obstetrician. A newborn with thrombocytopenia and an elevated NRBC at birth with delayed NRBC clearance (>48 hours) supports a hypoxic-ischemic event that is *remote* from delivery. Hematologic findings that are frequently found in newborns with a partial prolonged pattern of injury occurring *within hours of delivery* include an elevated NRBC count, a decreased platelet count starting 12 to 24 hours after an insult, and a nadir platelet count at 48 to 72 hours of age. A newborn with an acute profound injury associated with a sentinel event and an acute onset of severe fetal bradycardia for at least *10 to 15 minutes just before birth* most frequently has a normal CBC. A CBC may also be a useful laboratory test to diagnose other causes of NE such as anemia or infection/inflammation.

Hematologic values in newborns with NE provide additional information to approximate timing and duration of injury. These readily available laboratory results, along with the maternal history, fetal heart rate tracings, placental pathology, cord blood gases, Apgar score, newborn physical examination, and neuroimaging, provide some evidence to support or refute allegations of intrapartum asphyxia. For newborns with NE, we recommend that neonatal providers check a CBC/differential count soon after birth and daily for 3 to 7 days; such hematologic testing may provide insight into the diagnosis and timing of NE.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes and pathophysiology, including cellular abnormalities, of chronic asphyxia syndromes (eg, chronic fetal hypoxia and placental insufficiency).

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Thrombocytopenia in the Newborn

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Education Gaps

1. Knowing the differential diagnosis and most likely etiologies of thrombocytopenia in the neonate will lead to more appropriate diagnostic evaluations and treatments.
2. Thrombocytopenia may be a symptom of various congenital or acquired conditions in the neonatal period and should prompt further diagnostic evaluations.

Abstract

Neonates develop thrombocytopenia from a multitude of causes, including immune-mediated conditions, infections, inherited disorders, and acquired conditions such as thrombosis. This can make it challenging to diagnose an underlying cause and the evaluation can be extensive. This article will provide strategies to facilitate the evaluation of thrombocytopenia in the newborn and provide a background for the underlying pathophysiology of this condition and its various causes.

Objectives After completing this article, readers should be able to:

1. Provide a differential diagnosis for thrombocytopenia in the nursery or NICU.
2. Discuss the management of thrombocytopenia in the neonate.
3. Explain the differences between thrombopoiesis in the neonate compared with older children.
4. Describe the difference between neonatal autoimmune and alloimmune thrombocytopenia.
5. Discuss acquired conditions of thrombocytopenia (eg, disseminated intravascular coagulopathy, thrombosis).
6. Provide a differential diagnosis of inherited forms of neonatal thrombocytopenia.

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ABBREVIATIONS

CAMT	congenital amegakaryocytic thrombocytopenia
DIC	disseminated intravascular coagulation
HPA	human platelet antigen
ICH	intracranial hemorrhage
IVIG	intravenous immunoglobulin
NAIT	neonatal alloimmune thrombocytopenia
NEC	necrotizing enterocolitis
TAR	thrombocytopenia–absent radii
WAS	Wiskott-Aldrich syndrome
XLT	X-linked thrombocytopenia

THROMBOPOIESIS IN THE NEWBORN

Platelets were first described as discrete particles *"piastrine"* by Italian physician Giulio Bizzozero; since then, we have learned a great deal about these molecules that are key for hemostasis and thrombosis. Megakaryocytes produce platelets in a complex process that is stimulated by thrombopoietin. In neonates, megakaryopoiesis starts with megakaryocyte precursors circulating in both the blood and bone marrow, rather than solely in the bone marrow as in adults. Megakaryocytes undergo a maturation process in which they increase their DNA content and develop polyploidy (8N-64N). These mature megakaryocytes then generate and release new platelets into the circulation.

Megakaryocytes that have a higher ploidy produce more platelets. In the neonate, megakaryocytes generally are smaller in size and have lower ploidy. Many cytokines (interleukins 3, 6, 11) and chemokines (stromal cell–derived factor and fibroblast growth factor 4) are involved in megakaryopoiesis, but thrombopoietin is the most potent stimulator. Thrombopoietin is produced in the liver and has different effects on neonatal and adult megakaryocytes. Thrombopoietin stimulates polyploidization in adult megakaryocytes, hence increasing platelet production. In the neonate, thrombopoietin inhibits polyploidization, and megakaryocytes are even more sensitive to its stimulation. Because neonates have a normal platelet count, this means that the megakaryocytes and their progenitors have a very high proliferative potential to compensate the innate challenges of the neonatal megakaryocyte. Reticulated platelets are another emerging field of investigation in neonatal megakaryopoiesis. These are newly released platelets (24 hours old) that contain residual RNA and can be detected via flow cytometry. Another test, the percentage of the immature platelet fraction, is the percentage of reticulated platelets equivalent and is being investigated for clinical use to determine bone marrow response.

It is important to understand the differences between neonatal and adult megakaryopoiesis. One major distinction is that neonates lack reserve in their platelet production potential. Thus, when various causes lead to platelet consumption (eg, viruses, necrotizing enterocolitis [NEC], and disseminated intravascular coagulation [DIC]), the neonate can develop thrombocytopenia. This review will also discuss immune and nonimmune causes of thrombocytopenia.

DEFINITION AND INCIDENCE OF NEONATAL THROMBOCYTOPENIA

The presence of thrombocytopenia is highly variable in newborns, with the prevalence being significantly higher in sick infants. Thrombocytopenia is defined as a platelet count less than $150\times10^3/\mu L$ ($150\times10^9/L$). Overall, thrombocytopenia occurs in fewer than 1% of all newborns, but the highest prevalence occurs in the NICU (20%–35%), especially in very low-birthweight preterm neonates (70%–80%). Severe neonatal thrombocytopenia is typically defined as a platelet count less than $50\times10^3/\mu L$ ($50\times10^9/L$) and has been associated with significant clinical implications such as intracranial hemorrhage (ICH) and pulmonary or gastrointestinal bleeding.

Thrombocytopenia in preterm infants is very common and is frequently due to prenatal complications (pregnancy-induced hypertension, intrauterine growth restriction, placental insufficiency). In these situations, the platelet count usually is not in the severe range (ie, typically greater than $50\times10^3/\mu L$ [$50\times10^9/L$]) and spontaneous resolution occurs by 2 weeks of age. Perinatally acquired infections (eg, cytomegalovirus, group B *Streptococcus*) and severe perinatal hypoxia are also frequent culprits, often associated with DIC. These perinatal insults typically cause thrombocytopenia within the first 72 hours of age. Postnatally acquired infections or complications such as NEC precipitate thrombocytopenia after 72 hours of age. Although term infants can also have thrombocytopenia from all of the aforementioned reasons, neonatal alloimmune thrombocytopenia (NAIT) is the most common cause of thrombocytopenia in a healthy full-term infant and usually resolves within a week. If thrombocytopenia persists for more than 7 to 10 days in the well infant, congenital abnormalities, bone marrow failure syndromes, and other disorders have to be included in the differential.

PLATELET FUNCTION AND GUIDELINES FOR PLATELET TRANSFUSIONS

Platelets are short-lived cells, with a half-life of 7 to 10 days. The primary function of platelets is to prevent bleeding by maintaining endothelial integrity and forming platelet aggregates. Hence, if platelets are not functioning properly or are decreased in number, the clinical manifestations are bleeding, bruising, or petechiae. The bleeding is primarily mucocutaneous, but ICH can occur, particularly in preterm infants.

National guidelines typically recommend platelet transfusions to maintain platelet counts greater than 20 to $50\times10^3/\mu L$ ($20–50\times10^9/L$); however, this is based on expert opinion and consensus evidence rather than prospective, randomized, controlled trials. For preterm infants, the concern for bleeding is even higher and the causes of thrombocytopenia are typically associated with a higher bleeding risk (eg, DIC, NEC, infection). While the goal of treating thrombocytopenia in a neonate is to prevent a life-threatening hemorrhage, there is little evidence showing that certain platelet thresholds will prevent bleeding. To our knowledge, there is only 1 prospective study (Andrew et al) that investigated if transfusing platelets would decrease the incidence of ICH. The inclusion criteria for this study only involved very low-birthweight neonates with moderate thrombocytopenia ($50-150\times10^3/\mu L$ ($50-150\times10^9/L$)) in the first week after birth and this degree of thrombocytopenia did not have a negative impact on the outcomes of intracranial bleeding. Guidelines to help the clinician with decision-making should be based on platelet count, health of the neonate, and bleeding history.

- In general, if a neonate has a platelet count that is less than $20\times10^3/\mu L$ ($20\times10^9/L$), the neonate should receive a platelet transfusion, regardless of age or clinical condition.
- If a neonate has a platelet count that is less than $30\times10^3/\mu L$ ($30\times10^9/L$), indications to transfuse platelets include weight less than 1 kg, age less than 1 week, clinical instability, history of major bleeding (eg, IVH), current active bleeding, coagulopathy/DIC, need for surgery or invasive procedures.
- If a neonate has a platelet count that is greater than $50\times10^3/\mu L$ ($50\times10^9/L$), recommendations are to transfuse platelets for significant bleeding only.

Further prospective studies are needed in neonates, including neonates with severe thrombocytopenia, to help clinicians determine the safest and most effective interventions in critically ill neonates.

CAUSES OF THROMBOCYTOPENIA AND APPROACH TO THROMBOCYTOPENIA IN THE NEONATE

The causes of neonatal thrombocytopenia are broad and to determine the diagnosis, the clinician must consider the health of both the mother and infant, the infant's gestational age, complications of delivery, the current clinical state of the neonate (healthy vs ill), and the severity of the thrombocytopenia. The Table reviews the differential diagnosis of neonatal thrombocytopenia.

Thrombocytopenia can be caused by both inherited and acquired causes, and the diagnostic evaluation could be very extensive, so it is important to obtain the relevant information. Key factors that need to be considered are the onset of thrombocytopenia (early thrombocytopenia is defined as <72 hours of age and late thrombocytopenia is defined as 72 hours after birth), gestational age of the patient (term vs preterm), maternal history, severity of thrombocytopenia, the health status of the infant, family history of thrombocytopenia, and the presence or absence of congenital malformations. Figures 1, 2, and 3 have simplified algorithms of the approach to a differential diagnosis for preterm infants (based on early and late development of thrombocytopenia) and term infants.

Both term and preterm infants can become critically ill and develop thrombocytopenia as a result of consumption from complications such as infection, hypoxia, meconium aspiration, respiratory distress syndrome, NEC, and thrombosis. The sick newborn needs to be supported through the illness, receive platelet transfusion for indications that have been described before, and be evaluated to identify the underlying condition. If a sick neonate has a platelet count less than $50\times10^3/\mu L$ ($50\times10^9/L$), sepsis, DIC, or NAIT, are all possible diagnoses. Thrombocytopenia will not resolve for at least 5 to 7 days until the underlying condition has resolved.

Mild thrombocytopenia ($50-149\times10^3/\mu L$ [$50-149\times10^9/L$]) often occurs following fetal distress from chronic intrauterine hypoxia. This is a broad category and the most common causes are pregnancy-induced hypertension and/or fetal intrauterine growth restriction. Neonatal thrombocytopenia associated with placental insufficiency is commonly from chronic intrauterine hypoxia and is evident immediately after birth; this can be accompanied by other hematologic abnormalities such as transient neutropenia and increased numbers of circulating nucleated red cells. The severity of the placental insufficiency directly correlates with the degree of thrombocytopenia, but usually the platelet count is greater than $50\times10^3/\mu L$ ($50\times10^9/L$) and resolves within 14 days. If the degree of thrombocytopenia is more severe, or the recovery time is longer than expected, additional investigation is required. If there is no evidence of placental insufficiency, the neonatologist should ask about a family history of thrombocytopenia, check the maternal platelet count, and assess for any stigmata of a congenital syndrome such as thrombocytopenia–absent radii (TAR) syndrome, Fanconi anemia, trisomy 13, 18, 21, or Turner syndrome.

The most common reason for a healthy newborn to develop severe thrombocytopenia is NAIT, which is attributed to an immune-mediated destruction of fetal and neonatal platelets. Maternal antibodies cross the placenta to destroy fetal platelets expressing a paternal human platelet antigen (HPA) that the mother lacks. Other more rare causes of severe thrombocytopenia include vascular malformations and renal vein thrombosis.

The sections below include a brief overview of the most common causes of thrombocytopenia in newborns—immune-mediated (NAIT), abnormal production of platelets, or consumption of platelets due to acquired disorders (thrombosis, sepsis).

DIAGNOSIS AND MANAGEMENT OF NAIT

NAIT can have a dramatic presentation in an otherwise well neonate who has petechiae, bruising, and even significant bleeding (ICH). The pathophysiology includes an HPA

TABLE. Differential Diagnosis of Thrombocytopenia Based on Severity and Timing of Onset of Condition

MECHANISM	CATEGORIES	DIFFERENTIAL DIAGNOSES	SEVERITY	ONSET
Increased destruction of platelets	Immune	Neonatal alloimmune thrombocytopenia	Severe	Early
		Autoimmune thrombocytopenia (maternal immune thrombocytopenic purpura, systemic lupus erythematosus)	Severe-moderate	Early
		Drug-dependent antibodies (penicillin and derivatives, vancomycin, metronidazole)	Variable	Late
	Nonimmune	Necrotizing enterocolitis	Severe-moderate	Late
		Placental insufficiency (preeclampsia, eclampsia, pregnancy-induced hypertension)	Mild-moderate	Early
		Perinatal asphyxia	Severe	Early
		Sepsis	Severe	Variable
		Congenital thrombotic thrombocytopenic purpura (rare)	Severe	Variable
		Thrombosis (renal vein thrombosis, line-associated thrombosis)	Moderate	Variable
		Vascular tumor (Kasabach-Merritt syndrome, hepatic hemangioendothelioma)	Moderate	Variable
		Extracorporeal membrane oxygenation	Variable	Variable
Decreased production of platelets	Chromosomal disorders	Aneuploidies (trisomy 13, trisomy 18, trisomy 21, Turner syndrome)	Variable	Early
Decreased production of platelets	Inherited platelet disorders	Disorders with large platelets (eg, MYH-9 related disorders, Bernard-Soulier)	Variable	Early
		Disorders with small platelets (eg, Wiskott-Aldrich syndrome, X-linked thrombocytopenias)		
		Disorders with normal sized platelets (eg, congenital amegakaryocytic thrombocytopenia, thrombocytopenia absent radii syndrome)		
	Metabolic syndromes	Isovaleric acidemia	Mild-moderate	Variable
		Ketotic glycinemia		
	Bacterial	eg, Group B *Streptococcus*, gram-negative rods, *Staphylococcus*	Variable	Variable
	Fungal	eg, *Candida*	Severe	Early
	Viral	Cytomegalovirus, herpes simplex virus, human immunodeficiency virus, enteroviruses	Variable	Early
	Parasites	Toxoplasmosis	Variable	Early

mismatch between the infant's mother and father. In NAIT, fetal platelets that exhibit a paternal antigen that is distinct from the maternal platelet antigen cross the placenta and induce a maternal response with the production of maternal antiplatelet antibodies. These are immunoglobulin G antibodies, and can cross the placenta into the fetus, leading to platelet destruction and fetal and neonatal thrombocytopenia. NAIT typically leads to severe thrombocytopenia and up to 20% of neonates can have an ICH with 50% occurring in utero. It is crucial to diagnose NAIT because subsequent pregnancies can be affected. NAIT can develop in the first pregnancy of an at-risk couple and subsequent pregnancies can have even more significant bleeding.

The diagnosis of NAIT is made by demonstrating platelet antigen incompatibility between the mother and the neonate. This can be done in 2 ways: detection of maternal anti-HPA antibodies in the infant's circulation or HPA genotype mismatch between the infant and mother. All children who are diagnosed with NAIT should have genotyping of both the mother and father. In white populations, 95% of NAIT occurs from a mismatch in HPA-1a or HPA-5b, and the remaining 5% is due to anti-HPA-2, -3 or -15. Black patients have a much higher gene frequency of HPA-2b and HPA-5b, while the incidence of HPA-1b is much lower than in whites. Additional research needs to be done to elucidate the differences in HPA across ethnicities.

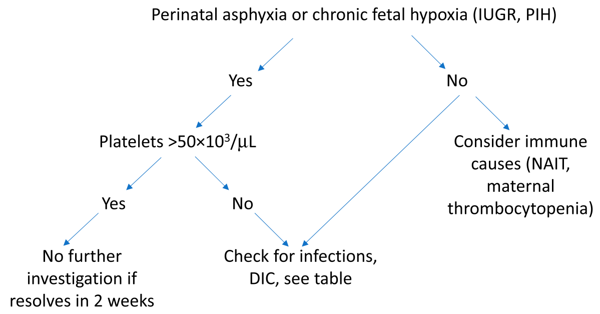
Perinatal asphyxia or chronic fetal hypoxia (IUGR, PIH)
Yes
No
Platelets >50×10³/µL
Consider immune causes (NAIT, maternal thrombocytopenia)
Yes
No
No further investigation if resolves in 2 weeks
Check for infections, DIC, see table

Figure 1. Differential diagnosis for early-onset (<72 hours of age) thrombocytopenia ($<150\times10^3/\mu L$ [$150\times10^9/L$]) in preterm neonates. DIC=disseminated intravascular coagulopathy; IUGR=intrauterine growth restriction; NAIT=neonatal alloimmune thrombocytopenia; PIH=pregnancy induced hypertension.

All neonates with suspected NAIT should be screened for ICH with head ultrasonography because ICH can have significant neurologic sequelae. If a newborn's platelet count is less than $30\times10^3/\mu L$ ($30\times10^9/L$) or if there are signs of bleeding, the ideal treatment for a neonate with NAIT is to provide HPA-1a-negative and 5b-negative platelets from the blood bank. Random donor platelets can be effective even though they will likely have the inciting antigen. Maternal platelets can only be used if they are washed because circulating antibodies will also be present.

In conjunction with platelet transfusions, intravenous immunoglobulin (IVIG) can be helpful in the management of NAIT in neonates. The proposed mechanism of action of IVIG in this disease involves inhibition of peripheral immune platelet destruction, but the pathophysiology has not been fully elucidated. After IVIG administration, it usually takes about 36 hours for the neonate to demonstrate a response in platelet count. Platelet counts need to be monitored until they return to normal levels. Infants with NAIT need to be followed by a hematologist after discharge from the NICU. If the mother is interested in becoming pregnant in the future, it is recommended that both she and her obstetrician be informed of the risks of NAIT in future pregnancies. During subsequent pregnancies, antenatal treatment of NAIT is important to decrease the risk of bleeding complications, especially because the majority of ICH occurs before birth. A recent systematic review by Winkelhorst et al suggests that first-line antenatal management is weekly maternal IVIG administration, with or without the addition of corticosteroids. There is a high complication rate (11%) of antenatal management with fetal blood sampling and intrauterine platelet transfusions, including fetal loss.

DIAGNOSIS AND MANAGEMENT OF NEONATAL AUTOIMMUNE THROMBOCYTOPENIA

Maternal autoantibodies arising from autoimmune conditions (immune thrombocytopenic purpura or systemic lupus erythematosus) can also cause thrombocytopenia in neonates because of the transplacental passage of maternal antibodies to the fetus. These antibodies typically do not cause the same degree of neonatal thrombocytopenia. Because the antibodies also affect maternal platelets, the mother's platelet count is low. Family history can help to establish this diagnosis, but many women are asymptomatic

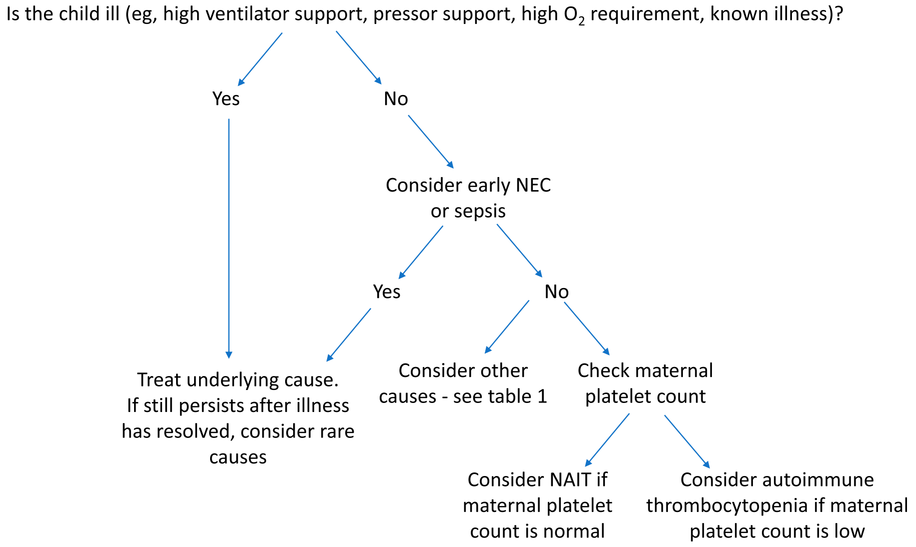
Is the child ill (eg, high ventilator support, pressor support, high O₂ requirement, known illness)?
Yes
No
Consider early NEC or sepsis
Yes
No
Treat underlying cause. If still persists after illness has resolved, consider rare causes
Consider other causes - see table 1
Check maternal platelet count
Consider NAIT if maternal platelet count is normal
Consider autoimmune thrombocytopenia if maternal platelet count is low

Figure 2. Differential diagnosis for late-onset (>72 hours) thrombocytopenia ($<150\times10^3/\mu L$ [$150\times10^9/L$]) in preterm neonates. NAIT=neonatal alloimmune thrombocytopenia; NEC=necrotizing enterocolitis.

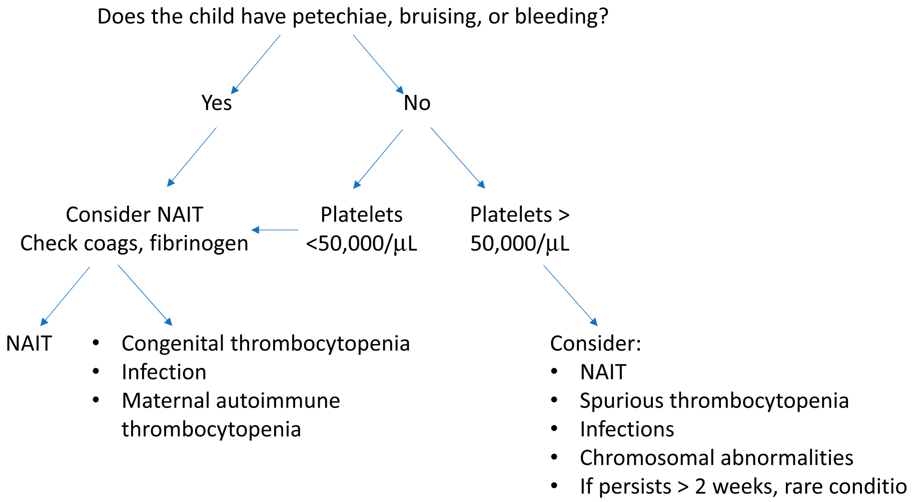
Does the child have petechiae, bruising, or bleeding?
Yes
No
Consider NAIT
Check coags, fibrinogen
Platelets
<50,000/µL
Platelets >
50,000/µL
NAIT
• Congenital thrombocytopenia
• Infection
• Maternal autoimmune thrombocytopenia
Consider:
• NAIT
• Spurious thrombocytopenia
• Infections
• Chromosomal abnormalities
• If persists > 2 weeks, rare conditio

Figure 3. Differential diagnosis for thrombocytopenia ($<150\times10^3/\mu L$ [$150\times10^9/L$]) in full-term neonates. NAIT=neonatal alloimmune thrombocytopenia.

and unaware of a potential disorder. If a pregnant woman has a known autoimmune condition associated with thrombocytopenia, a platelet count should be obtained on the infant after delivery. A neonate with thrombocytopenia associated with maternal autoimmune disease requires a supportive management approach; if there is severe neonatal thrombocytopenia or bleeding, IVIG and/or platelet transfusions may be needed.

DECREASED PRODUCTION OF PLATELETS: INHERITED THROMBOCYTOPENIAS

Disorders of Small Platelets

Wiskott-Aldrich Syndrome and X-linked Thrombocytopenia. Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia (XLT) are both inherited X-linked microthrombocytopenia syndromes that are caused by mutations in the WAS protein (*WASP*) gene on the short arm of the X chromosome. The WAS protein is important in the cytoskeleton of megakaryocytes and T lymphocytes. WAS is a syndrome that is characterized by immunodeficiency, eczema, microthrombocytopenia, and development of autoimmune conditions and malignancy. Early recognition is important so that affected patients can be placed on bacterial and fungal prophylaxis. XLT is a less severe form of WAS and patients usually have isolated microthrombocytopenia. Genetic defects in the WAS gene that lead to absent or markedly decreased expression lead to the WAS phenotype, while individuals with missense mutations with partial expression of WAS have the XLT phenotype. Currently, the only cure for WAS is bone marrow transplantation, but small studies have shown eltrombopag, a thrombopoietin mimetic, can improve thrombocytopenia in patients with both WAS and XLT.

Disorders of Normal-Sized Platelets

1. Congenital Amegakaryocytic Thrombocytopenia. Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare recessive autosomal disorder that typically presents shortly after birth. Most affected infants have severe thrombocytopenia with petechiae, bruising, or bleeding. Most patients with CAMT have mutations in the *c-mlp* gene, the receptor for thrombopoietin, and hence, have a markedly reduced number of megakaryocytes. CAMT typically presents with isolated thrombocytopenia, but affected children are at high risk for developing complete bone marrow failure in the first few years of age. Bone marrow transplantation is currently the only curative option.

2. TAR Syndrome. This syndrome is characterized by bilateral absence of the radii and the presence of thrombocytopenia. Recently, 2 genetic mutations have been found in the majority of patients: microdeletion on chromosome 1q21 and 2 rare single nucleotide polymorphisms in the *RBM8A* gene. This syndrome results from impaired reactivity to thrombopoietin in the hematopoietic stem and progenitor cells, as well as megakaryocytes. The underlying pathophysiology to explain the association of thrombocytopenia and absent radii still needs to be elucidated. Severe thrombocytopenia occurs shortly after birth, and affected neonates frequently have bleeding. Other physical abnormalities have also been described in patients with TAR including cardiac, urogenital, and other skeletal abnormalities. In patients with TAR, both thumbs are present, in contrast to the skeletal abnormalities of children with Fanconi anemia, another bone marrow failure syndrome. In most children with TAR, the platelet count will improve after 2 years of age, even to almost normal values of $100\times10^3/\mu L$ ($100\times10^9/L$). Until resolution of the thrombocytopenia, affected patients require supportive treatment with platelet transfusions as needed.

In patients with Fanconi anemia with missing radii, the thumbs are also absent, which is an important morphologic difference between Fanconi anemia and TAR syndrome.

3. Familial Platelet Disorder with a Propensity for the Development of Acute Myelogenous Leukemia. This is a rare autosomal dominant disorder characterized by thrombocytopenia, aspirinlike functional platelet defect, and propensity to develop myelodysplastic syndrome and acute myelogenous leukemia. Mutations involving *RUNX1* lead to arrest of megakaryocyte maturation with an expanding population of progenitor cells. A family history of myelodysplastic syndrome or acute myelogenous leukemia should raise suspicion for this disorder in a newborn with thrombocytopenia or significant bleeding.

Disorders of Large Platelets

1. Bernard-Soulier Syndrome. Bernard-Soulier syndrome is caused by a deficiency of the GPIb/IX/V complex on platelets, which binds to von Willebrand factor. Mutations for this condition are on chromosomes 17, 22, and 3. A homozygous deficiency is characterized by severe thrombocytopenia, giant platelets, inability for ristocetin-induced platelet aggregation, and significant clinical bleeding. Heterozygotes may have milder macrothrombocytopenia and less bleeding. The diagnosis of Bernard-Soulier syndrome is confirmed by the absence of CD41a or PGPIb-IX-V on flow cytometry. Treatment for Bernard-Soulier syndrome is mostly supportive and platelet transfusions may be needed for life-threatening bleeding.

2. *MYH9*-Related Disorders. Nonmuscle myosin heavy chain type IIa (*MYH9*) mutations cause macrothrombocytopenia and are found in several different syndromes (May-Hegglin anomaly, Fechtner syndrome, Sebastian syndrome, and Ebstein syndrome). May-Hegglin anomaly is characterized by the presence of leukocyte Dohle-like inclusion bodies in the neutrophils and is a rare cause of fetal or neonatal ICH. The defect in May-Hegglin anomaly is in the *MYH9* gene on chromosome 22q.

3. Acquired Consumptive Disorders: Kasabach-Merritt Syndrome. Kasabach-Merritt syndrome is a life-threatening consumptive coagulopathy in the presence of a rapidly enlarging vascular tumor. It usually presents in early infancy with a phenomenon of coagulopathy, DIC, and microangiopathy that is associated with a vascular malformation. Fifty percent of patients with a vascular tumor present with this phenomenon and it is important to start treatment early to prevent life-threatening hemorrhage or anemia. Treatment involves supportive care and aggressive management with steroids. Sirolimus, a mechanistic target of rapamycin inhibitor, has demonstrated significant improvements in high-risk patients with these vascular lesions.

THROMBOTIC DISORDERS

The incidence of venous thromboembolism is rising, especially in the neonatal population. The incidence of venous thromboembolism in children has increased from 34 to 58 per 10,000 hospital admissions in recent years. Because of the need for central catheters and the increased complexity of neonatal care, the incidence of venous thromboembolism is even higher, at 75 per 10,000 hospital admissions in infants younger than 28 days. Heparin-induced thrombocytopenia and arterial thrombosis are increasing concerns, though still quite rare in pediatrics. Thrombocytopenia and renal failure should prompt investigation for a renal vein thrombosis with Doppler ultrasonography. Treatment for thrombotic conditions in a neonate can be complicated by consumption of platelets at the time of thrombosis, hence making treatment challenging.

CONCLUSIONS

Neonatal thrombocytopenia is extremely common and has a broad differential. It is important to factor in the timing of the thrombocytopenia, prenatal and maternal history, severity of the thrombocytopenia, and overall health of the infant. Although infection is the most common reason for early neonatal thrombocytopenia in sick infants, NAIT is the most common cause for well children. Treatment of neonatal thrombocytopenia is mainly supportive. The mechanisms underlying thrombocytopenia in a neonate typically take several weeks to resolve and will need to be followed by a pediatrician. It is important to keep a broad differential, and a hematologist evaluation may be warranted for children with persistent thrombocytopenia.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the normal pattern of platelet production and maturation.
- Know the causes and pathophysiology of neonatal thrombocytopenia and thrombocytosis.
- Know the clinical and laboratory manifestations and management of neonatal thrombocytopenia and thrombocytosis.

Suggested Readings

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Thrombocytopenia in the Newborn

Kerry Morrone

NeoReviews 2018;19;e34
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Index of Suspicion in the Nursery

1 A Well-Growing Neonate with Features of Intestinal Obstruction

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AUTHOR DISCLOSURE Drs Jain, Bharadwaj, and Ramji and Mr Agarwal have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

CASE PRESENTATION

A 1,555-g, first of twin female infants is born at 38 4/7 weeks to a 24-year-old primigravida in a vaginal delivery through clear amniotic fluid. The infant is small for gestational age (<10th percentile on the Fenton intrauterine growth chart) with features of intrauterine malnutrition, such as triangular facies and loose skinfolds. The antenatal period is uneventful. The infant needs only basic steps at birth, with Apgar scores of 9, 9, and 9 at 1, 5, and 10 minutes, respectively. In view of the low birthweight, the neonate is transferred to the NICU and placed under the warmer with servo skin mode. Full tube feeding is initiated under observation.

The infant passes meconium on the first postnatal day at 18 hours of age and has a normal stool transition. She tolerates feeds well until day 6 after birth, with an expected weight loss of 1.2% per day. On the sixth postnatal day, she has abdominal distention (an increase in girth of 3 cm) with multiple episodes of vomiting. On evaluation, she is found to be euthermic (temperature of 98.9°F [37.2°C]), euglycemic (glucose concentration of 64 mg/dL [3.5 mmol/L]), normocalcemic (calcium concentration of 4.04 mg/dL [1.01 mmol/L]), with no evidence of any systemic illness. Hence, surgical causes like volvulus, Hirschsprung disease, meconium ileus, and acute/subacute intestinal obstruction are the most likely considerations in the differential diagnosis. A sepsis evaluation is nonsuggestive (total leukocyte count 7,600/μL [7.6×10^9/L]; absolute neutrophil count 3,400/μL [3.4×10^9/L]; micro–erythrocyte sedimentation rate 10 mm/h; immature to total neutrophil ratio 0.16). The abdominal radiograph is suggestive of gaseous distention with no air fluid levels (Figs 1 and 2).

In view of the persistent signs, despite normal findings, feeding is withheld and intravenous fluids are started, with continuous nasogastric aspiration with a 6F feeding tube. The rectal stimulation results in no improvement. On postnatal day 8, under strict asepsis, a glycerin saline enema (20 mL glycerin with 20 mL saline) is administered to the neonate under the supervision of the pediatric surgeon. The enema results in passage of greenish-yellow, pasty, putty, long stool plugs (Fig 3). Subsequently, the obstruction is relieved, and a normal stooling pattern observed. Feeding is resumed and a consistent weight gain with breastfeeding is noted in the following week. The infant is discharged on the 13th postnatal day. A follow-up at 14 weeks reveals normal growth and development with no complaints.

CASE DISCUSSION

After a thorough literature search, a diagnosis of inspissated milk syndrome with no recurrence was strongly considered in this case.

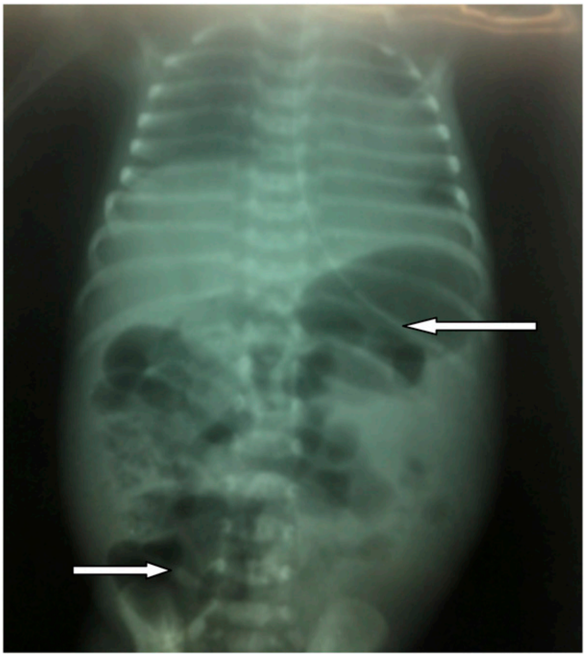

Figure 1. Abdominal radiograph of a supine infant showing gas-filled abdomen with nonsignificant findings.

The Condition

Inspissated milk syndrome is also known as *lactobezoar, milk bolus syndrome,* or *milk curd syndrome,* and has been reported in both the Indian and western literature. (1)(2) The best proposed etiopathogenesis of this condition is differential absorption of water and solid nonfats in the milk, leading to precipitation with mucous in the gastrointestinal tract. Several host and environmental factors have been proposed as predisposing newborns to this condition. Some of the most important factors are prematurity, low birthweight, overconcentrated formula (calorie content of >80 kcal/kg), high casein content (>60%), high calcium content, use of special preterm formulas, and use of breast milk fortifiers. (1)(3) In the current case, the inspissation developed in a term and exclusively breastfed neonate. Hence, even though formula feeding and prematurity are reported to be associated and predisposing infants to milk bolus syndrome, they may not represent the primary pathology involved. Most infants present within 2 to 10 days after birth with features suggestive of acute obstruction, such as abdominal distention, vomiting, and gastric residues, as seen in the current case. The condition is seldom reported to present with abdominal mass.

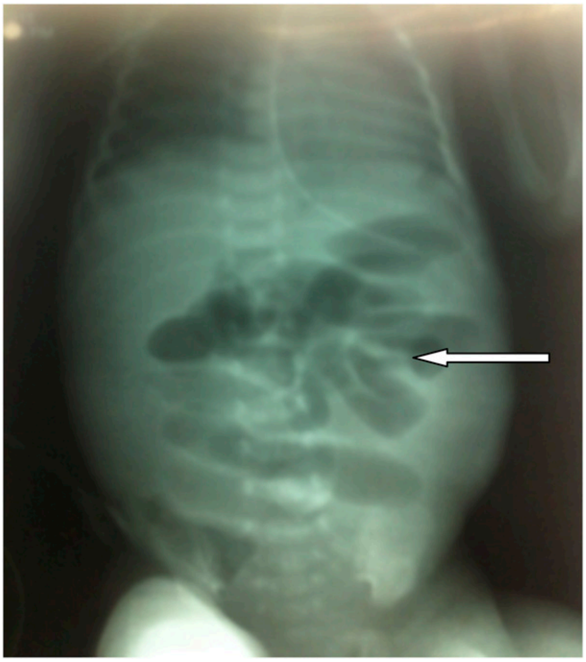

Figure 2. Abdominal radiograph of an upright infant showing gas-filled abdomen with absence of fluid air levels.

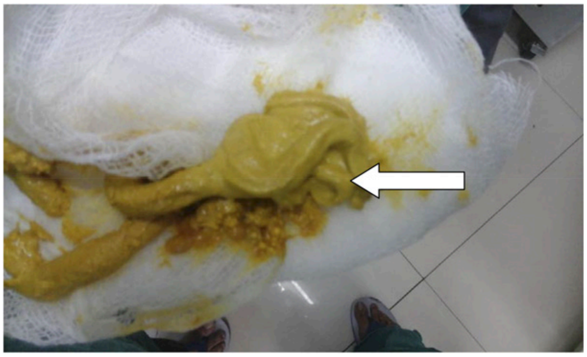

Figure 3. Photograph of a long, inspissated stool, which is passed as greenish yellow, pasty, long stool plugs.

Diagnosis

In most cases, radiology is nonspecific and does not help in the diagnosis. Various radiologic findings reported include absent gas shadow in right lower quadrant and air fluid levels in the small bowel, as seen in obstruction. Occasionally, specific findings like gastric mass with an air halo around it or fecal mass in the lower gut with a bubbly appearance and air trapped within have also been reported. Abdominal ultrasonography may show a free-floating intragastric mass or intrabezoaric echogenic foci suggestive of trapped air. In cases of lactobezoar located in the stomach (*gastric lactobezoars*), radiography may offer a specific clue because it is seen as a moving mass with a change in the patient's posture. (3) A sincere effort should always be made to rule out more sinister and common causes of acute intestinal obstruction like volvulus, intussusception, Hirschsprung disease, and meconium ileus.

After ruling out the common causes, a high index of suspicion in an "apparently well infant with features of acute intestinal obstruction" is essential to diagnose inspissated milk syndrome.

Treatment

Most cases of inspissated milk syndrome respond to conservative management. This includes gut rest, intravenous fluids, and gastric decompression. Gastrograffin or N-acetyl cysteine gastric lavage, gastroscopic disintegration, and removal have also been used with variable success in gastric lactobezoars. (2)(3) Enema can be useful in cases with inspissation involving the lower part of the gut as in the current case. Occasionally, changes in milk formula alone have resulted in rapid improvement. The success of conservative treatment clearly argues against primary invasive measures. However, caution is warranted when the cause of acute abdomen remains elusive for more than 24 hours.

Rarely, in complications like perforation and when conservative management fails, surgical intervention is required.

Most of these infants are well, with an uneventful follow-up after the acute episode is relieved. One case of recurrence has been reported in a 30-week-old preterm neonate with tracheoesophageal fistula, who was started on formula feeding postoperatively; however, that infant was later diagnosed as having celiac disease. (4)

Lessons for the Clinician

- The diagnosis of inspissated milk syndrome requires a high index of suspicion in a relatively well infant suspected to have acute intestinal obstruction.
- Although this condition can occur in any infant, it is more common in preterm infants receiving high-calorie and/or fortified formula.
- The condition is usually managed conservatively, resulting in rapid resolution and a very good prognosis.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the factors that may inhibit or improve intestinal motility.

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Case 1: A Well-Growing Neonate with Features of Intestinal Obstruction

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2 A Patient with Trisomy 21, Transient Abnormal Myelopoiesis, and Pneumoperitoneum

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AUTHOR DISCLOSURE Drs Barkhuff, Camacho, McKee, and Stefanescu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 34-week-gestation male infant is born appropriate for gestational age to a 41-year-old gravida 3, para 3 woman. The patient's mother had received limited prenatal care starting at 15 weeks, and is found to have a positive result on maternal serum α-fetoprotein screening test and an amniocentesis that confirms trisomy 21 (47,XY+21 karyotype) with no evidence of translocation or mosaicism. The infant is born at an outside hospital and has physical features characteristic of trisomy 21. He is transferred to our facility for respiratory distress and multiple episodes of apnea and bradycardia on the day of birth. Sepsis is ruled out on admission. His initial complete blood cell count is significant for a white blood cell count of 15,300/μL (15.3×10^9/L) with 25% blasts. He is also noted to have an enlarged liver that is 1 cm below the costal margin. Peripheral blood smear and flow cytometry findings are consistent with a diagnosis of transient abnormal myelopoiesis (TAM). Pediatric hematology is consulted and recommends complete blood cell counts which are obtained regularly until day 22 after birth, when the TAM spontaneously resolves.

The infant is able to receive full enteral feedings until he develops abdominal distention and irritability on day 12 after birth. An abdominal radiograph is notable for pneumoperitoneum concerning for an acute bowel perforation without signs of pneumatosis intestinalis (Fig 1). A blood culture specimen is obtained and he is started on antibiotics. A nasogastric tube is placed for gastric decompression while the infant is stabilized with appropriate fluid replacement and is given nothing per mouth. Immediately before surgery, he develops acute cardiopulmonary compromise requiring intubation, mechanical ventilation, and inotropic support. Surgical exploration reveals that the bowel appears viable. There is significant inflammation in the right lower quadrant and fibrinous exudate around the cecum. The appendix appears quite inflamed with an obvious area of perforation (Fig 2). An appendectomy is performed. The histopathologic evaluation of the resected specimen shows neutrophilic exudate (Fig 3). This confirms the diagnosis of acute appendicitis and periappendicitis.

Immediately after surgery, the infant requires multiple normal saline boluses and inotropic support. His blood culture and peritoneal fluid culture are positive for *Escherichia coli* and *Klebsiella pneumoniae*. Cerebrospinal fluid culture and gram stain are negative. He continues to require intubation for 4 days after

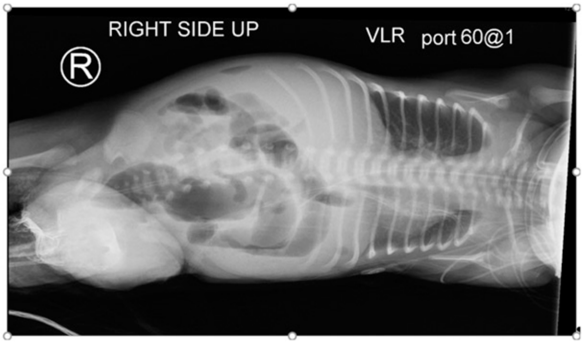

Figure 1. Abdominal radiograph showing gaseous distention of the bowel with free intraperitoneal air on day 12 after birth.

surgery, and gradually weans to low-flow nasal cannula. Feeds are gradually resumed and he achieves full enteral feedings by 28 days after birth. His postoperative course is also complicated by a surgical site infection that develops on postoperative day 7. The infant completes a 14-day antibiotic course. He is discharged from the NICU on day 39 to the general pediatric department to work on oral feedings. He is discharged from the hospital 1 week later on low-flow nasal cannula and full oral feedings with a recommendation to return for pediatric hematology and pediatric pulmonology follow-up as an outpatient. He is seen by pediatric hematology and pediatric pulmonology at 2.5 months' chronologic age and advised to get monthly complete blood cell counts until age 24 months and to gradually wean off nasal cannula oxygen at home during the day. He will continue follow-up with these specialists as an outpatient.

DISCUSSION

Several cases of neonatal appendicitis have been described in the literature with few of them in premature infants. However, it is considered to be a rare occurrence, with an incidence of 0.04% to 0.2%. Acute appendicitis is therefore rarely considered in the differential diagnosis of acute abdomen in neonates. However, it is associated with higher morbidity and mortality rates in neonates than in older children. Acute appendicitis in neonates is often associated with prematurity, congenital abdominal defects, cystic fibrosis, or Hirschsprung disease. Neonates may be at low risk for appendicitis for several reasons: the neonatal appendix has a wide opening to the cecum, the diet is liquid, infants are often kept in recumbent position, and infections are generally infrequent.

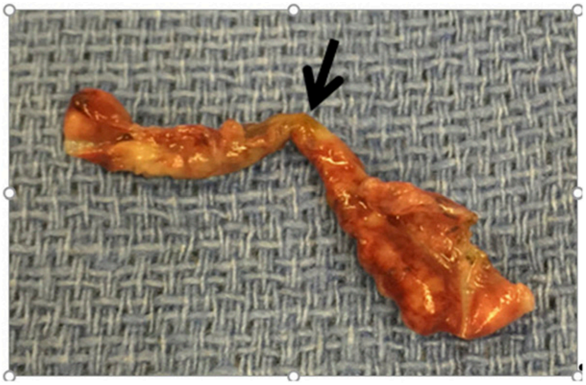

Figure 2. Gross appearance of the appendix showing inflammation and an area of perforation (arrow).

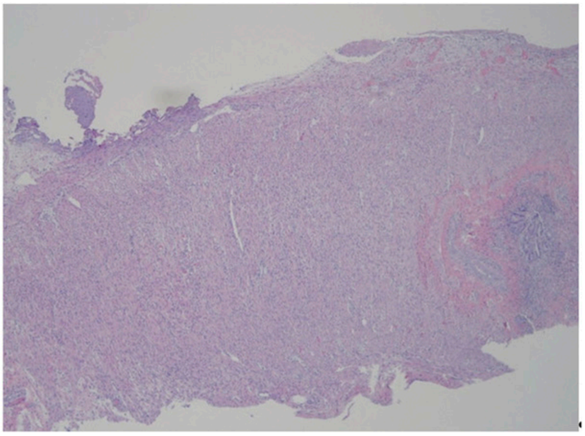

Figure 3. Histopathology slide of the appendix showing neutrophilic infiltration and inflammation.

Other than prematurity at 34 weeks, comorbidities usually associated with neonatal appendicitis were not found in our case. Particularly in the case of preterm neonates, there is debate about whether neonatal appendicitis is actually necrotizing enterocolitis (NEC) affecting the appendicitis or classic appendicitis. In the case of this patient, NEC would be a much more likely diagnosis given the infant's prematurity and the relative incidences of each entity in the neonatal period. However, on surgical exploration, an obvious area of perforation was noted in the appendix and the surrounding bowel appeared normal, supporting the diagnosis of classic appendicitis.

Given the low risk of appendicitis in a patient with trisomy 21 with no risk factors, we wonder if TAM could have predisposed this patient to appendicitis. Lymphoid hyperplasia is known to be the most common pathologic finding associated with acute appendicitis, though it is unclear whether this finding is the cause or effect of acute appendicitis. Development of lymphoid hyperplasia in the periappendiceal region, which could occur during the natural course of TAM, could have caused the obstruction of the appendiceal opening into the cecum with subsequent perforation.

Another unusual aspect of this case is that a decreased incidence of appendicitis has been reported in patients with trisomy 21 compared with the general population, which lowered the index of suspicion for diagnosis.

Lessons for the Clinician

- This may be the first case report of an infant with trisomy 21, TAM, and perforation of the appendix. A search of the literature did not uncover a similar case.
- A perforated appendix in preterm infants is associated with high mortality.
- A possible association between TAM and acute appendicitis may exist in infants with trisomy 21, and therefore, physicians need to maintain a strong clinical suspicion. Early institution of supportive therapies such as appropriate fluid management, gastrointestinal decompression, antibiotic therapy, and surgical consultation and intervention, when necessary, can significantly improve outcomes.

ACKNOWLEDGMENT

Special thanks to Drs Jodi Mayfield and Kathleen Madden for their thoughtful review of this case report.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the clinical manifestations, diagnosis, and management of infants with perforations of the gastrointestinal tract (including gastric and intestinal).

Suggested Readings

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Parent Resources from the AAP at HealthyChildren.org

- **Children with Down Syndrome: Health Care Information for Families:** https://www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Children-with-Down-Syndrome-Health-Care-Information-for-Families.aspx

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at http://patiented.aap.org.

Case 2: A Patient with Trisomy 21, Transient Abnormal Myelopoiesis, and Pneumoperitoneum

Whittney Barkhuff, Jenny Camacho, Jason McKee and Beatrice M. Stefanescu

NeoReviews 2018;19;e45

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Index of Suspicion in the Nursery

3 An Infant with Severe Dehydration, Weight Loss, and Abnormal Newborn Screening Test Results

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AUTHOR DISCLOSURE Drs Was, Lee, Nally, and Arain have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant is born at 37 weeks' gestation via vaginal delivery to a gravida 4, para 3 woman. The woman's pregnancy and delivery are uncomplicated. The infant's birthweight is 2,680 g. She is discharged from the hospital in good condition; at home, she breastfeeds well and gains weight appropriately; on day 10, her weight is 2,778 g (4% above birthweight).

On day 12, the mother notes that the infant has begun to breastfeed poorly. On day 14, formula feeding is attempted, but her intake remains poor, with an associated decrease in urine output. On day 16, she presents to an outpatient clinic, where she appears cachectic and severely dehydrated but responsive. Her weight is 1,760 g, a decrease of more than 1 kg (37%) from 6 days ago. She is transferred to the NICU for further evaluation and treatment.

The infant's newborn screening results from day 1 are normal; however, repeat newborn screening performed on day 10 shows an abnormality in the fatty acid oxidation profile, with malonyl carnitine levels of 0.68 μmol/L (normal ≤0.5 μmol/L). The patient's initial laboratory tests were notable for the following results: sodium, 174 mEq/L (174 mmol/L); potassium, 7.2 mEq/L (7.2 mmol/L); chloride, 141 mEq/L (141 mmol/L); bicarbonate, 7 mEq/L (7 mmol/L); blood urea nitrogen, 273 mg/dL (97 mmol/L); creatinine, 5.61 mg/dL (428 μmol/L); glucose, 1,266 mg/dL (70.2 mmol/L); anion gap, 31 mEq/L (31 mmol/L); lactate, 40.5 mg/dL (4.5 mmol/L); ammonia, 83 μg/dL (59 μmol/L); β-hydroxybutyrate, 3.1 mmol/L (reference range 0.2–2.8 mmol/L); serum osmolality, 433 mOsm/kg (433 mmol/L); white blood cells, 9,500/μL (9.5×10^9/L); hemoglobin, 19.7 g/dL (197 g/L); platelets, 33×10^3/μL. C-peptide level was 1.1 ng/mL (0.36 nmol/L; reference range 0.8–4 ng/mL [0.26–1.32 nmol/L]) when blood glucose was 477 mg/dL (26.4 mmol/L) while receiving an intravenous insulin infusion. Subsequent therapeutic intervention confirmed the diagnosis.

DISCUSSION

Diagnosis

The patient required an intravenous insulin infusion of up to 0.04 U/kg per hour (~1 U/kg per day) for treatment of severe hyperglycemia. She received fluid resuscitation for dehydration and correction of hypernatremia. The hypernatremia was attributed to severe dehydration from osmotic diuresis due to glycosuria. Over the course of several days, with insulin infusion and fluid restoration, her electrolytes and glucose levels stabilized (Figure).

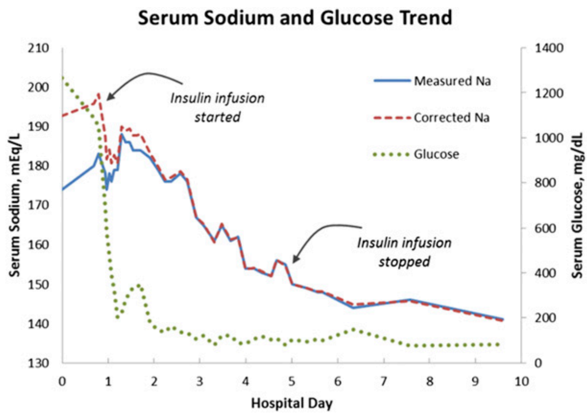

Figure. Serum sodium (Na) and glucose trend.

The infant received platelet and blood transfusions for thrombocytopenia and anemia. She developed rhythmic movements concerning for seizures and received lorazepam for treatment, but subsequent analysis with electroencephalography did not reveal seizure activity. The patient had no recurrence of symptoms. She was able to breastfeed and maintain normal glucose levels without administration of exogenous insulin, and was discharged in stable condition. Result of genetic testing for neonatal diabetes mellitus (DM) was negative. Diabetes autoantibodies in the infant and mother were negative.

The Condition

Neonatal DM is a rare metabolic disorder that usually presents in the first 6 months after birth; it is defined as persistent hyperglycemia in the first months after birth, which lasts at least 2 weeks and requires management with insulin. (1) The incidence of neonatal DM is approximately 1 in 300,000 to 400,000 newborns. Most cases of neonatal DM are monogenic in nature and result in poor insulin production. Clinically, patients are placed into 2 categories: transient and permanent. In transient neonatal DM, symptoms resolve during infancy, though there is a 50% chance for recurrence later in life. (2) In permanent neonatal DM, symptoms persist, and management depends on exogenous insulin. (3) The clinical presentation of hyperglycemia and low insulin may be accompanied by findings such as failure to thrive, dehydration, and/or ketoacidosis, as was seen in this patient. (4)

The case represents a nonclassic presentation of diabetes in early infancy with a negative genetic evaluation. The time frame of her hyperglycemia is unclear based on clinical history; however, the duration likely was longer than the 4 days during which she required insulin. Endogenous insulin production was present based on the detectable C-peptide level, though it was insufficient to overcome hyperglycemia. The C-peptide level confirmed that the infant was able to produce a very small amount of insulin, and that she did not have complete insulin deficiency. The patient's clinical course and history of low birthweight at term supports the diagnosis of transient neonatal DM; however, genetic evaluation for the most common causes of this condition was unrevealing. Unusual aspects of her presentation included the severity of hyperglycemia, with glucose levels up to 1,200 mg/dL (67 mmol/L), which was likely related to dehydration and poor renal perfusion. The serum osmolality was significantly elevated, suggesting a presentation of hyperosmolar hyperglycemia. The clinical picture of hypernatremia, hyperosmolality, hyperglycemia, and severe dehydration raises the possibility of Wolfram syndrome as a diagnosis, which involves DM, diabetes insipidus, anemia, and thrombocytopenia. (5) This particular case lacked the characteristics of hearing loss and optic atrophy, which could develop later in life.

Insulin administration and high caloric intake are crucial to ensure adequate growth in such patients. Total body water deficit should be slowly corrected to euvolemia, to prevent rapid fluid and electrolyte shifts. Because glucose predominantly exists in extracellular fluid, hyperglycemia results in extracellular hyperosmolarity, which requires osmotic equilibration achieved by water abstraction. Hyperglycemia, therefore, is known to depress serum sodium concentration. To accurately assess and manage sodium abnormalities, serum sodium levels should be corrected by using the Katz formula (6):

$$\begin{aligned}\text{Corrected Sodium (in mEq/L)} = {} & \text{Measured Sodium (in mEq/L)} \\ & + 0.016 \times (\text{Glucose [in mg/dL]}) \\ & - 100\end{aligned}$$

Hyperglycemia should be corrected slowly to avoid rapid changes in osmolarity. Similarly, serum sodium should be corrected at a rate of 0.5 mEq/L per hour, because of the risks of cerebral edema and seizures associated with rapid correction of hypernatremia. (7) Serum electrolytes and pH should be measured regularly during treatment of neonatal DM and ketoacidosis, to monitor for concurrent alterations of serum potassium, magnesium, calcium, bicarbonate, or phosphorus. (8)

Lessons for the Clinician

- Abnormal newborn screening test results should be interpreted with caution and relative to the clinical context. Alternative metabolic disease processes can cause false-positive results.
- Neonatal diabetes mellitus may present with severe dehydration, acidosis, and electrolyte abnormalities, which should be corrected slowly because of the danger of significant and rapid changes.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the impact on water requirements of renal and metabolic fluid disorders associated with endocrine dysfunction in infants.
- Know how to manage electrolyte abnormalities in the neonate.
- Know the causes, including genetic and autogenic disorders, of neonatal hyperglycemia, including transient diabetes mellitus.
- Know the clinical and laboratory features and approach to therapy of neonatal hyperglycemia, including transient diabetes mellitus.

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Parent Resources from the AAP at HealthyChildren.org

- **Newborn Screening Tests:** https://www.healthychildren.org/English/ages-stages/baby/Pages/Newborn-Screening-Tests.aspx

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Case 3: An Infant with Severe Dehydration, Weight Loss, and Abnormal Newborn Screening Test Results

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Head and Shoulder Trauma

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AUTHOR DISCLOSURE Dr Sims has disclosed that she has been compensated for reviewing records and providing testimony in some of the cases highlighted in Legal Briefs. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A 4,580-g, 38 5/7 weeks' gestation male infant was delivered by a 33-year-old gravida 5, para 1, aborta 1 woman whose pregnancy had been unremarkable. One month before delivery, the woman reported a decrease in fetal movement, but fetal activity resumed subsequently and the nonstress test result was normal. The pregnancy continued without problems. However, when labor began and the fetus did not descend, she received oxytocin to augment labor. Fetal tachycardia, decreased variability, and excessive uterine activity were noted. Also, inadequate rest time between contractions appeared as the second stage of labor was approaching. ***The plaintiff obstetrician pointed out that the fetus was being stressed since the peak of 1 contraction to the next peak should be at least 2 minutes, and the end of 1 contraction to the beginning of the next should be at least 1 minute. He also discussed that oxytocin should have been discontinued because of the lack of descent and the excessive uterine activity. The obstetrician retained by the defense said that technically tachysystole was not present and the tracing was category 2. He stated that the continuation of oxytocin was acceptable because the fetus was not descending adequately. The plaintiff obstetrician maintained that the tracings were concerning; the progression of labor was not appropriate; and it was clear, hours before delivery, that the pregnant woman could not safely deliver this fetus vaginally.*** Two and a half hours before delivery when the station was −1 and the cervix was fully effaced and dilated, the membranes were artificially ruptured. Thin, light brown, meconium-stained fluid was noted. ***The defense obstetrician said that the decreased fetal movement that had occurred previously at 34 weeks' gestation and the light brown meconium passage at the time of delivery suggested prior brain damage. The plaintiff experts disagreed and pointed out that the meconium passage probably was from stress during the labor. Furthermore, the plaintiff obstetrician noted that the fetus had been evaluated with a nonstress test when decreased fetal movement was reported. Also, fetal movement resumed to normal for the remainder of the pregnancy.*** As the woman began pushing during the second stage, fetal tachycardia increased further and some late and several deep variable decelerations occurred. The intrapartum course was complicated by shoulder dystocia. The obstetrician did a reverse Woods corkscrew rotation to facilitate the delivery.

The arterial cord gas had a pH of 7.18, partial pressure of carbon dioxide ($P\text{CO}_2$) of 56 mm Hg (7.45 kPa), partial pressure of oxygen ($P\text{O}_2$) of 19 mm Hg (2.5 kPa), and base excess of 8.2; the venous cord gas had a pH of 7.22, $P\text{CO}_2$of 52 mm Hg (6.9 kPa), $P\text{O}_2$ of 23 mm Hg (3 kPa), and base excess of 7.2. The nurse and respiratory therapist were called to the delivery after the infant was born because of apnea, hypotonia, and an ashen color. The team provided positive pressure ventilation followed by continuous positive airway pressure. The male infant was then brought to the NICU. He had a normal head circumference initially, but it increased as scalp swelling became more prominent; within a couple of hours, his head had massively increased in size.

Shortly after arriving in the NICU, the infant underwent intubation because of ineffective respirations. His first blood gas measurement at 40 minutes of age on low ventilator settings showed a pH of 7.16, $P\text{CO}_2$ of 28 mm Hg (3.7 kPa), $P\text{O}_2$ of 61 mm Hg

(8.1 kPa), and base excess of 17.2. His first blood pressure measurement was 29/33 mm Hg with a mean of 25 mm Hg. The blood pressure was obtained again after 50 mL of normal saline, and was 41/18 mm Hg with a mean of 25 mm Hg. He was started on antibiotics and was given normal saline boluses, inotropic support, and sodium acetate. His first hematocrit was 33%. He was given a packed red blood cell transfusion. His coagulation studies became abnormal. He continued to have generalized hypotonia. Skull radiography showed a fracture of the occipital bone. Computed tomography (CT) of his head was performed at 22 hours and showed a large cephalohematoma, a subgaleal hemorrhage, subdural hemorrhages, displacement of the occipital bone relative to the parietal bone with misalignment at the coronal and sagittal sutures, an area suspicious for temporal and occipital lobe infarction, and an occipital bone fracture. Neurosurgery was consulted and it was determined that the infant would not benefit from a surgical intervention. Magnetic resonance imaging (MRI) of the brain was performed at 4 days of age, which confirmed the CT findings.

Twenty-four hours after birth, the infant began having seizures and was given phenobarbital. He underwent extubation at 36 hours. When his generalized hypotonia lessened, it became obvious that his right upper extremity had decreased activity. An MRI scan of his cervical spine and right brachial plexus was obtained at age 2 weeks, and a right cervical nerve root avulsion was noted. He was discharged at age 6 weeks after a gastric tube was placed for feeding difficulties. He received physical and occupational therapy. On follow-up evaluations, the child could not use his right arm, and had developmental delays and cerebral palsy.

The obstetrician was sued. The case settled without going to trial.

DISCUSSION

Even under optimal circumstances, the process of birth is somewhat traumatic, but when additional labor and delivery challenges are present, the potential for hypoxic, ischemic, and mechanical damages in isolation or in various combinations is greater. The obstetrician must be vigilant of the lack of progressive descent and any cephalopelvic disproportion, and be judicious in the use of oxytocin. Most importantly, the obstetrician must know when to abandon hope for a safe vaginal delivery. When the fetus is especially large, malpositioned, or sending out signals through heart rate patterns or inadequate descent, the delivering physician must understand the vulnerability of the fetus when pursuing a vaginal delivery. When significant caput or molding occurs in the fetus during labor, vaginal examination may be misleading in terms of fetal station, thereby leading to misjudgments of station and descent progress. Moreover, although some fetal head molding contributes to satisfactory descent as the head accommodates for passage through the birth canal, excessive head molding may result in cranial birth injuries.

Significant resistance and repetitive pushing against the birth canal tissues, whether from cephalopelvic disproportion, malposition, or other etiology, can generate compressive and/or shear forces leading to head trauma. The trauma can be manifested by ischemic or hemorrhagic injury to the brain, by distortion of the tentorium and falx structures leading to subdural hemorrhage and compression of the brain, or by avulsion of the aponeurosis from the cranium creating a subgaleal hemorrhage. The latter can occur with any delivery that is mechanically challenged, but is especially associated with vacuum-assisted deliveries.

In addition to the cranium, body parts commonly affected by serious mechanical events during labor include the shoulders, resulting in Erb or Klumpke palsy. Less often, cervical spine injury, fractured arms or legs, and rarely, liver hemorrhage may occur with traumatic deliveries. Linear skull and clavicle fractures are the most common mechanically affected areas and are generally benign if in isolation. Infants born with head trauma without concomitant generalized hypoxemia may actually appear reasonably well immediately after birth until the cerebral edema leads to clinical symptoms such as apnea, seizures, lethargy, or poor feeding. Infants with head trauma resulting in large blood loss, especially subgaleal hemorrhages, need replacement with immediate blood transfusion to correct the hypovolemia. Brachial palsy injuries associated with a generalized hypoxic-ischemic insult may not be recognized until the tone and activity resume in an infant. Whenever the delivery is difficult, the neonatologist needs to have special vigilance for such delivery scenarios with prolonged second stage labor that includes lack of timely descent, instrumentation, malposition, and obstetrical manipulations.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical features and prognosis of birth injuries, such as fractures, lacerations, and facial palsies.

Suggested Readings

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Legal Briefs: Head and Shoulder Trauma

Maureen E. Sims

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Strip of the Month

Marked Variability: To Worry or Not?

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal values for arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

AUTHOR DISCLOSURE Drs Wolfe and Demasio have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. Arterial Umbilical Cord Gas Values

	pH	P_{CO_2} (mm Hg)	P_{O_2} (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤−10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤−10
Metabolic acidosis	<7.20	<60	Variable	≥−10
Mixed acidosis	<7.20	>60	Variable	≥−10

*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695.

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:
  - Absent: Amplitude range is undetectable
  - Minimal: Amplitude range is greater than undetectable to 5 beats/min
  - Moderate: Amplitude range is 6–25 beats/min
  - Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - ○ Normal: ≤5 contractions in 10 minutes
  - ○ Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:

  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:

  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:

  - Absent variability with any of the following:

    - ■ Recurrent late decelerations
    - ■ Recurrent variable decelerations
    - ■ Bradycardia

  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

PRESENTATION

History

A 27-year-old gravida 2, para 0-0-1-0 woman presents to the labor and delivery (L&D) department at 40 1/7 weeks' gestation with painful uterine contractions and 4 episodes of emesis. Her membranes were intact, but she reported bloody vaginal discharge earlier that morning. The fetal heart rate tracing (FHR) is shown in Fig 1.

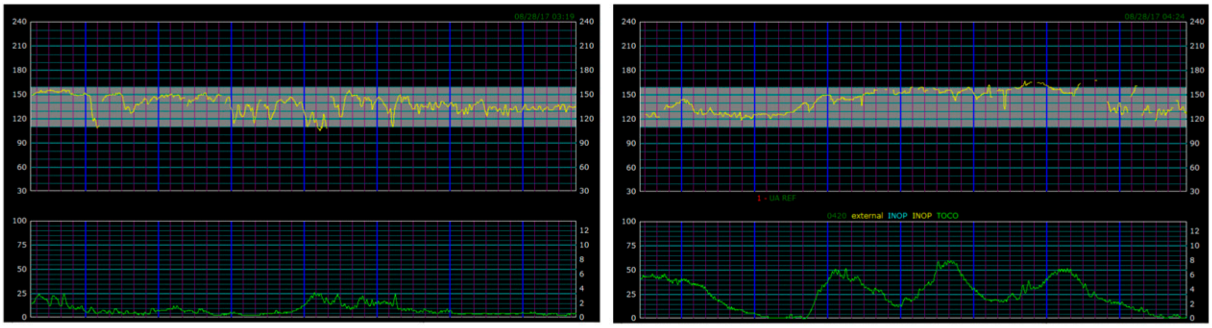

Figure 1. Electronic fetal monitoring strip 1.

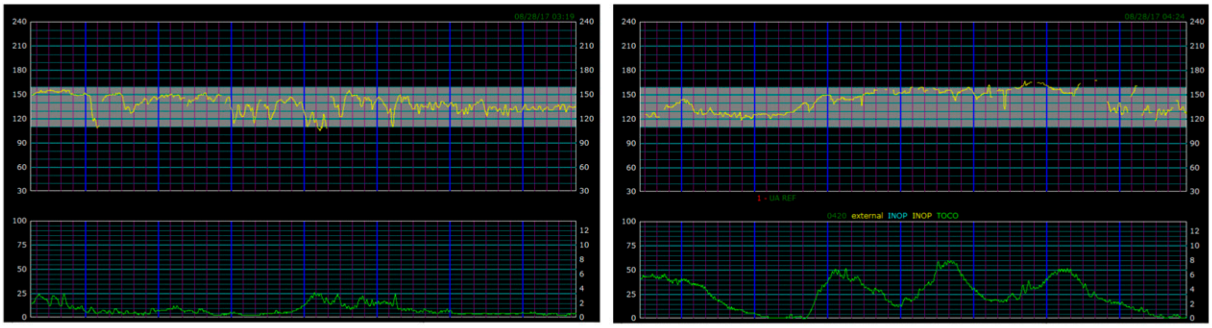

Figure 1. Electronic fetal monitoring strip 1.

Findings from electronic fetal monitoring strip 1 are as follows:

- Variability: Marked
- Baseline rate: 130 beats/min
- Episodic patterns: Marked variability
- Periodic patterns: Prolonged acceleration
- Uterine contractions: Every 2 to 3 minutes
- Interpretation: Category II tracing
- Differential diagnoses: Active labor, latent labor, fetal respiratory morbidity
- Action: Administer oxygen, place patient on left side

The prenatal course was significant for a prior hospitalization at 34 3/7 weeks' gestation when she had been referred to L&D by her obstetric provider for evaluation of preterm labor.

Upon her arrival at L&D, concern was raised about the fetal status due to the presence of "marked variability" on the FHR tracing (Fig 2). The 2 upper frames in the tracing do not show a clear baseline. FHR rounded to 5 beats/min for a minimum of 2 minutes in a 10-minute segment is required to establish the baseline. There were periods of FHR change from peak to trough of greater than 25 beats/min, which indicate marked variability.

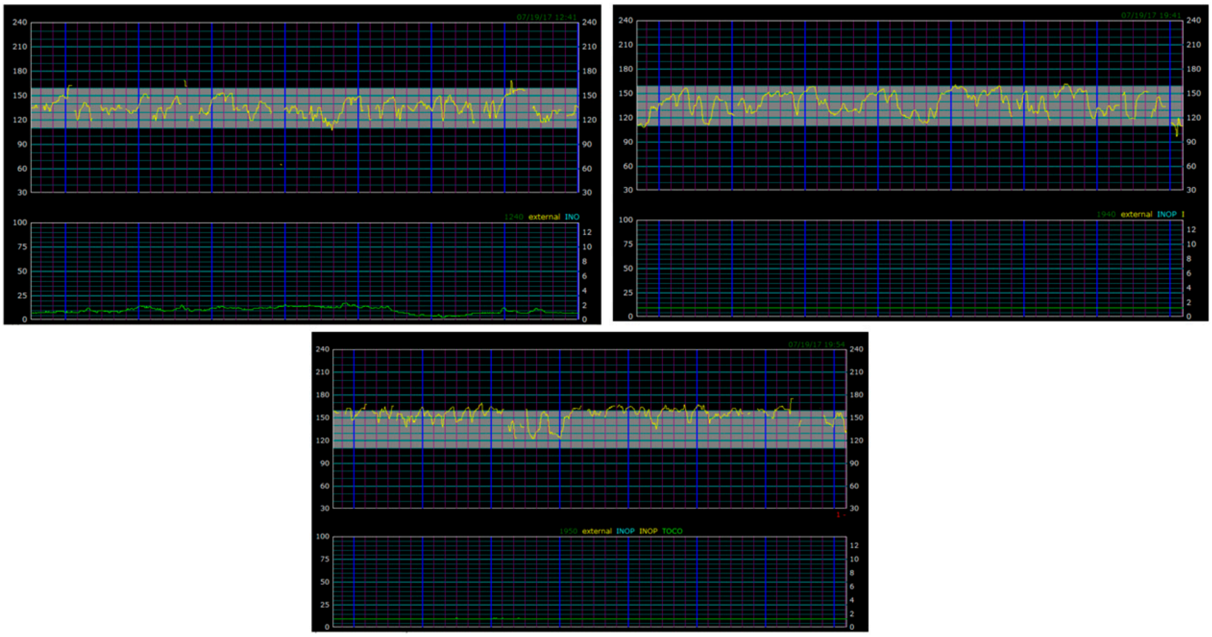

Figure 2. Electronic fetal monitoring strip 2.

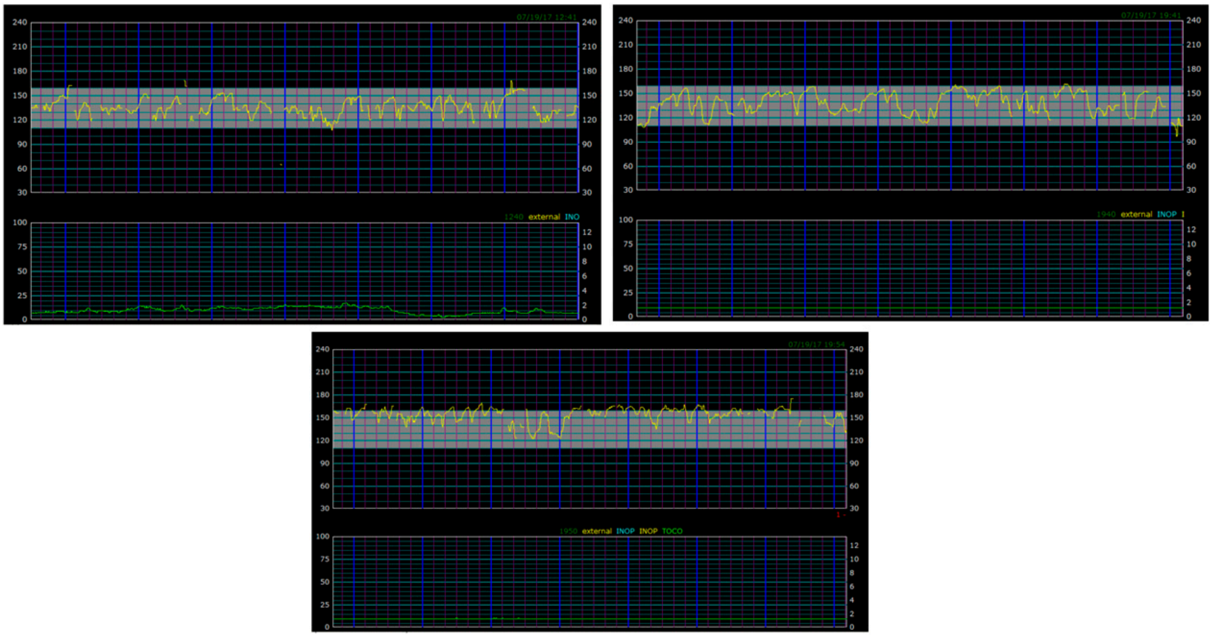

Figure 2. Electronic fetal monitoring strip 2.

Findings from electronic fetal monitoring strip 2 are as follows:

- Variability: Marked
- Baseline rate: Upper panels without a clear baseline
- Episodic patterns: Marked variability
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category II tracing
- Differential diagnoses: Preterm labor, fetal respiratory morbidity
- Action: Extended FHR monitoring

The decision was made to extend FHR monitoring to better assess the fetal well-being. Although the patient denied contractions, the cervix was dilated to 3 cm with 50% effacement at −3 station. The concern for preterm delivery within 7 days in this nulliparous woman led to the administration of antenatal corticosteroids to enhance fetal lung maturity. Prolonged monitoring led to the FHR tracing shown in Fig 3, and the fetal status was considered uninterpretable. Uterine activity was irregular and uterine irritability was noted.

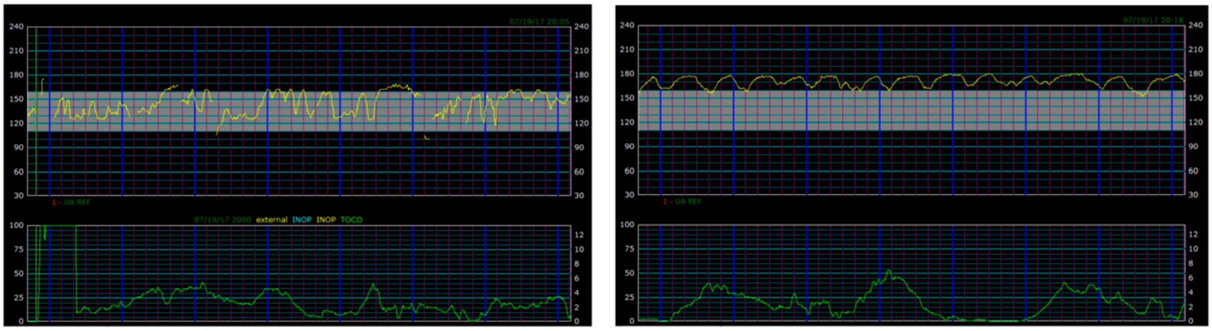

Figure 3. Electronic fetal monitoring strip 3.

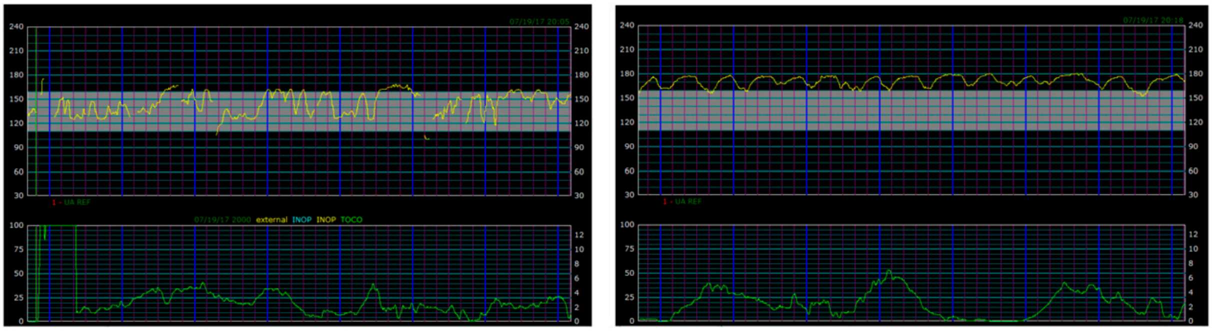

Figure 3. Electronic fetal monitoring strip 3.

Findings from electronic fetal monitoring strip 3 are as follows:

- Variability: Marked
- Baseline rate: 130 beats/min
- Episodic patterns: Marked variability, pseudosinusoidal pattern
- Periodic patterns: Fetal tachycardia
- Uterine contractions: Every 3 minutes
- Interpretation: Category II tracing
- Differential diagnoses: Preterm labor, fetal respiratory morbidity
- Action: Continued FHR monitoring and observation

The cervical examination remained the same and she continued to be observed without further intervention. The FHR tracing on hospital day 2 is shown in Fig 4. Episodic marked variability can be seen in frame 2, with return to category I tracing as seen in the lower frames. Uterine irritability resolved over time.

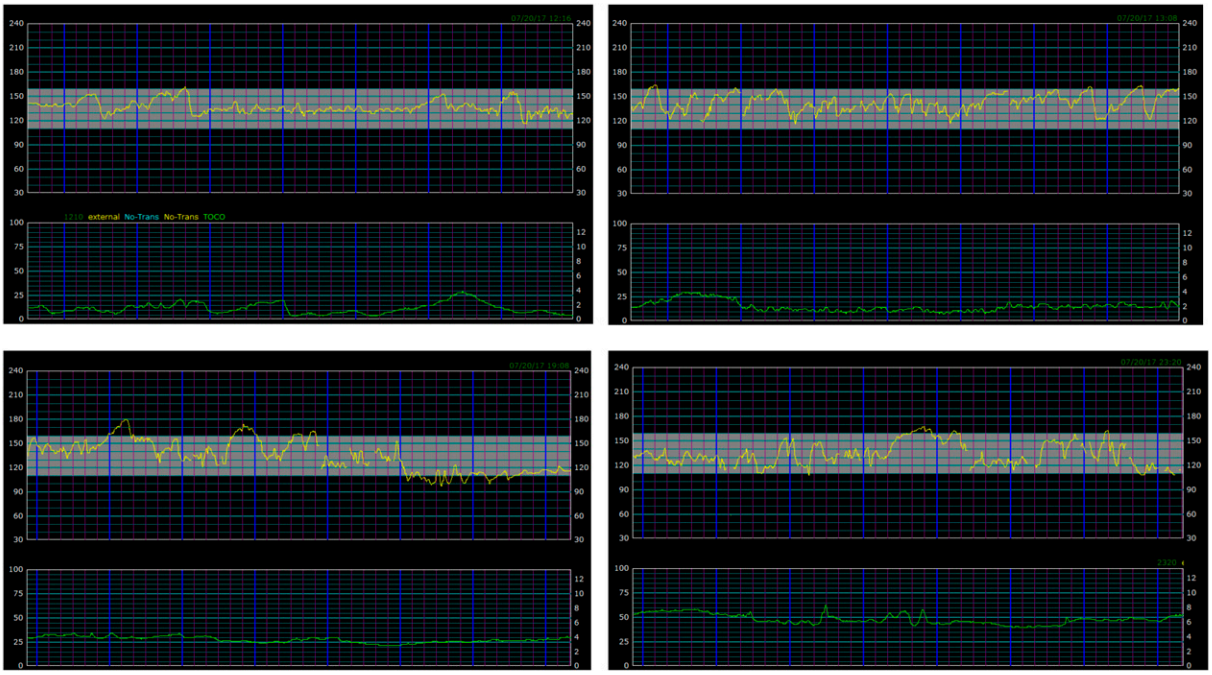

Figure 4. Electronic fetal monitoring strip 4.

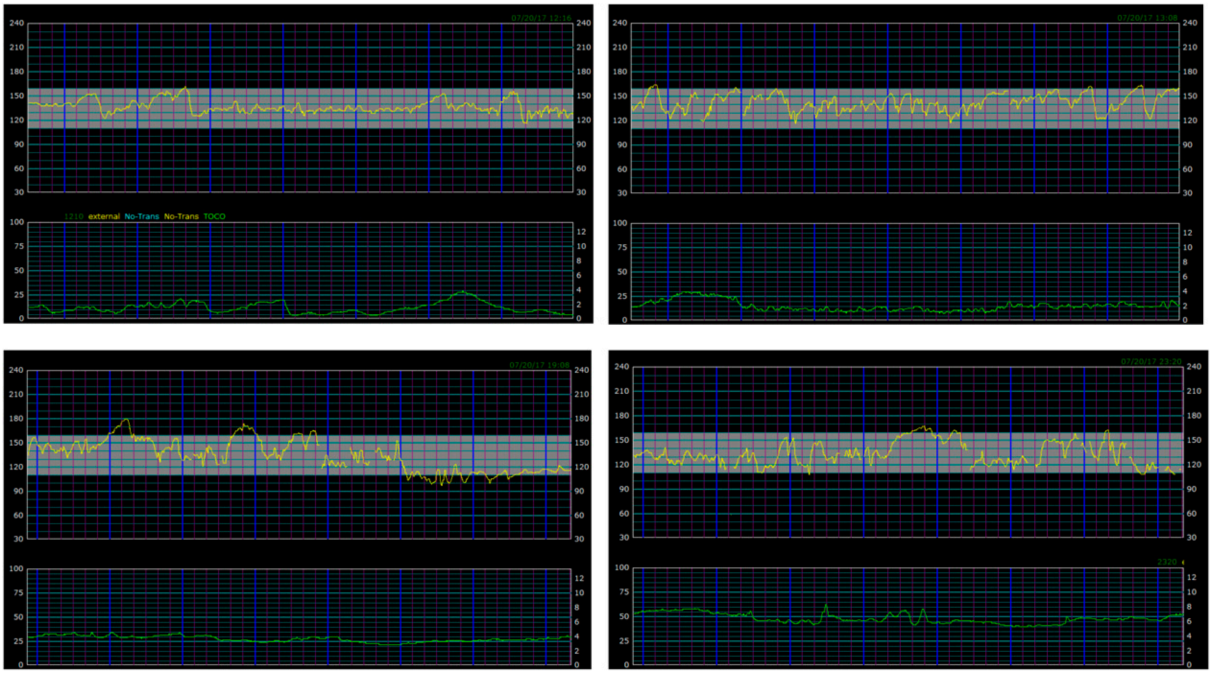

Figure 4. Electronic fetal monitoring strip 4.

Findings from electronic fetal monitoring strip 4 are as follows:

- Variability: Moderate
- Baseline rate: 130 beats/min
- Episodic patterns: Marked variability
- Periodic patterns: None
- Uterine contractions: Irritability
- Interpretation: Category I tracing
- Differential diagnoses: Reassuring fetal status
- Action: Continued fetal surveillance for cervical change

By hospital day 3, the overall tracing was reassuring (Fig 5).

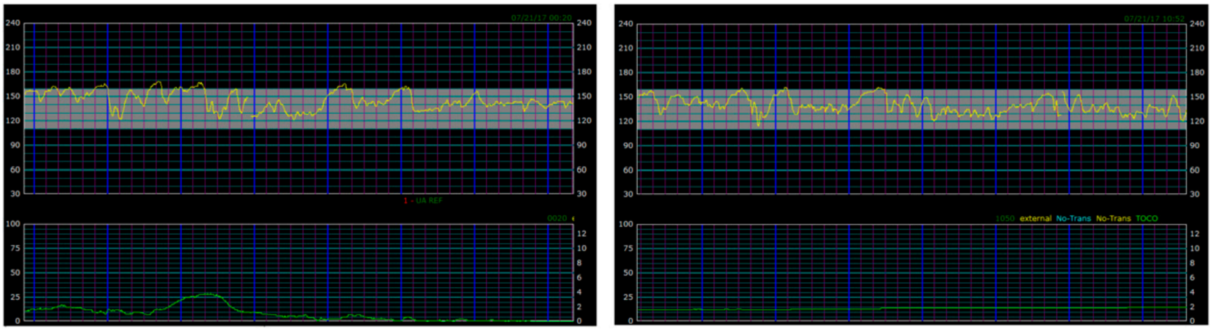

Figure 5. Electronic fetal monitoring strip 5.

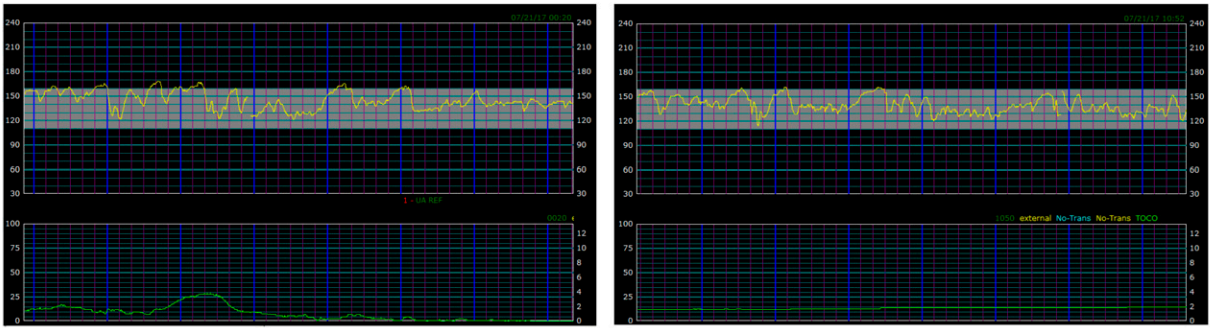

Figure 5. Electronic fetal monitoring strip 5.

Findings from electronic fetal monitoring strip 5 are as follows:

- Variability: Moderate
- Baseline rate: 140 beats/min
- Episodic patterns: Marked variability
- Periodic patterns: None
- Uterine contractions: Occasional contraction
- Interpretation: Category I tracing
- Differential diagnoses: Reassuring fetal status
- Action: Patient discharged from the hospital

The only medication the patient received was betamethasone. Because there was no further cervical change, a decision was made to discharge the patient from the hospital.

The woman's medical history was significant for bariatric surgery 4 years before this conception. She lost a total of 90 pounds and gained 20 pounds during this pregnancy. Her body mass index was 28 kg/m^2 at the initial prenatal visit and increased to 31 kg/m^2 at 40 1/7 weeks' gestation. She attended 18 prenatal visits and her prenatal laboratory values were unremarkable. She had a folate level greater than 20 ng/mL (45.3 nmol/L), vitamin B$_{12}$ concentration of 414 pg/mL (305.4 pmol/L), and a vitamin D concentration that was slightly decreased at 27.6 ng/mL (69 nmol/L). Her 1-hour glucose challenge test (GCT) result was 52 mg/dL (2.9 mmol/L) at approximately 6 weeks' gestation, and repeat screening administered at 26 1/7 weeks' gestation revealed a value of 137 mg/dL (7.6 mmol/L). Our institutional cutoff to complete the 3-hour glucose tolerance test (GTT) is 130 mg/dL (7.2 mmol/L), however the patient was unable to tolerate a 100-g GTT so diagnostic testing was not performed.

The woman was readmitted in spontaneous labor at 40 1/7 weeks' gestation and found to have elevated blood pressures during her labor. A category II tracing (Fig 6) was present.

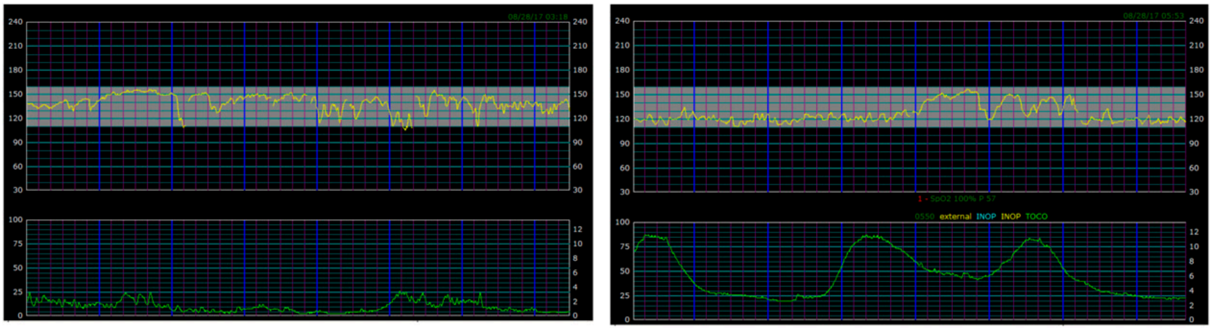

Figure 6. Electronic fetal monitoring strip 6.

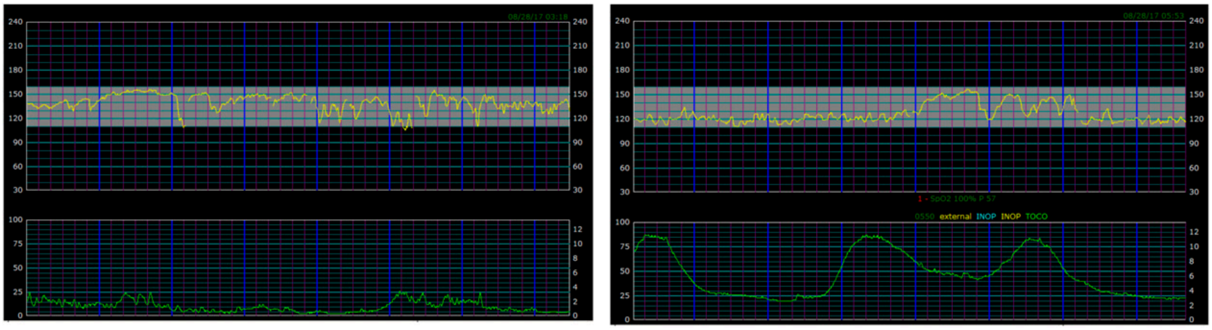

Figure 6. Electronic fetal monitoring strip 6.

Findings from electronic fetal monitoring strip 6 are as follows:

- Variability: Moderate
- Baseline rate: 120 beats/min
- Episodic patterns: Marked variability
- Periodic patterns: None
- Uterine contractions: Every 2 to 3 minutes
- Interpretation: Category I tracing
- Differential diagnoses: Labor, reassuring fetal status
- Action: Admit for spontaneous labor and delivery

She progressed while having episodes of moderate variability, which was thought to be reassuring for the fetal status. She had a spontaneous vaginal delivery, and a well-appearing male infant was delivered with an Apgar score of 9 at 1 and 5 minutes. The umbilical cord gases are illustrated in Table 2. The infant's birthweight was 2,950 g, and the infant was admitted to the newborn nursery.

DISCUSSION

Baseline variability is defined as fluctuations in the FHR of more than 2 cycles per minute. In the nomenclature put forth

TABLE 2. **Cord Blood Gases Demonstrate Mild Respiratory Acidosis Likely due to Normal Labor**

VARIABLE	PATIENT RESULT	REFERENCE RANGE
Arterial		
pH	7.171	7.35–7.45
P_{CO_2}, mm Hg (kPa)	59.2 (7.8)	35–45 (4.7–5.9)
P_{O_2}, mm Hg (kPa)	35.5 (4.7)	80–100 (11–13)
Base excess, mEq/L (mmol/L)	−6.5 (6.5)	−10 to −2 (−10 to −2)
HCO_3, mEq/L (mmol/L)	20.8 (20.8)	22–28 (22–28)
Hematocrit, %	47.5	42–60
Direct O_2 saturation, %	67.4	94–100
Venous		
pH	7.206	7.350–7.450
P_{CO_2}, mm Hg (kPa)	60.5 (8)	35–45 (4.7–5.9)
P_{O_2}, mm Hg (kPa)	24.5 (3.2)	80–100 (11–13)
Base excess, mEq/L (mmol/L)	−3.7 (3.7)	−10 to −2 (−10 to −2)
HCO_3, mEq/L (mmol/L)	23.1 (23.1)	22–28 (22–28)
Hematocrit, %	46.8	42–60
Direct O_2 saturation,	41.5	94–100

HCO_3=bicarbonate; O_2=oxygen; P_{CO_2}=partial pressure of carbon dioxide; P_{O_2}=partial pressure of oxygen

by the NICHD, there is no distinction between short-term (beat-to-beat variability or R-R wave period differences on fetal electrocardiography [ECG]) and long-term variability. Grades of fluctuation are based on the range of amplitude (peak to trough). Marked variability is defined by a fluctuation grade greater than 25 beats from peak to trough, and has been used to describe FHR patterns since the early use of fetal ECG in the 1970s. The actual significance of marked variability as it pertains to fetal oxygenation is not well described, and whether there should be concern about the fetal status is not known. Rather, marked variability is denoted as a category II FHR tracing—indeterminate and not predictive of abnormal acid-base status. (1)

In a prospective cohort study, FHR pattern 2 hours before the delivery of term singleton, nonanomalous fetuses whose mothers were in labor were extracted and analyzed to determine their association with neonatal respiratory morbidity. Respiratory morbidity was defined as neonatal oxygen requirement after the first 6 hours after birth or mechanical ventilation in the first 24 hours after birth. The prevalence of this outcome in their term cohort was low, at 3.7%. However, it was reported that fetuses with baseline tachycardia or marked variability were significantly more likely to have respiratory morbidity. The adjusted odds ratios were 2.9 and 2.7, respectively. (2) In the present case, the representative segments of the FHR tracing in the 2 hours before delivery are shown in Fig 7. Although episodes of marked variability were seen in this category II FHR tracing, intermittent periods of moderate variability were reassuring and labor was allowed to progress because the pattern is predictive of normal fetal acid-base status. This term neonate did not require oxygen.

Bariatric surgery before pregnancy can impose maternal nutritional deficiencies such as vitamin B_{12}, folate, iron, vitamin D, and calcium. If there is a proven deficit, then appropriate treatment should be instituted and monitored. Furthermore, in the absence of a deficiency, monitoring the complete blood cell count, iron level, ferritin, calcium, and vitamin D levels every trimester may be considered. (3) An understanding of the specific bariatric surgical procedure is helpful to determine the risk for intestinal malabsorption. The digestion and absorption of nutrients in the gastrointestinal tract requires complex interactions among motor, secretory, digestive, and absorptive processes that are vulnerable to surgical disturbances, and may lead to global or specific malabsorption syndromes. (4) The sleeve procedure in this patient was a partial gastrectomy in which a portion of the stomach was removed. She was treated with both iron and vitamin D supplementation because of low levels of these nutrients. Although she was unable to tolerate the GCT to establish a diagnosis of gestational diabetes, there was no evidence of a fetal effect of maternal hyperglycemia. The fetus had grown appropriately, and had an uncomplicated neonatal course. Prior bariatric surgery has not been shown to alter the labor course and therefore, this history was unlikely to contribute to the marked variability of this fetus. (3)

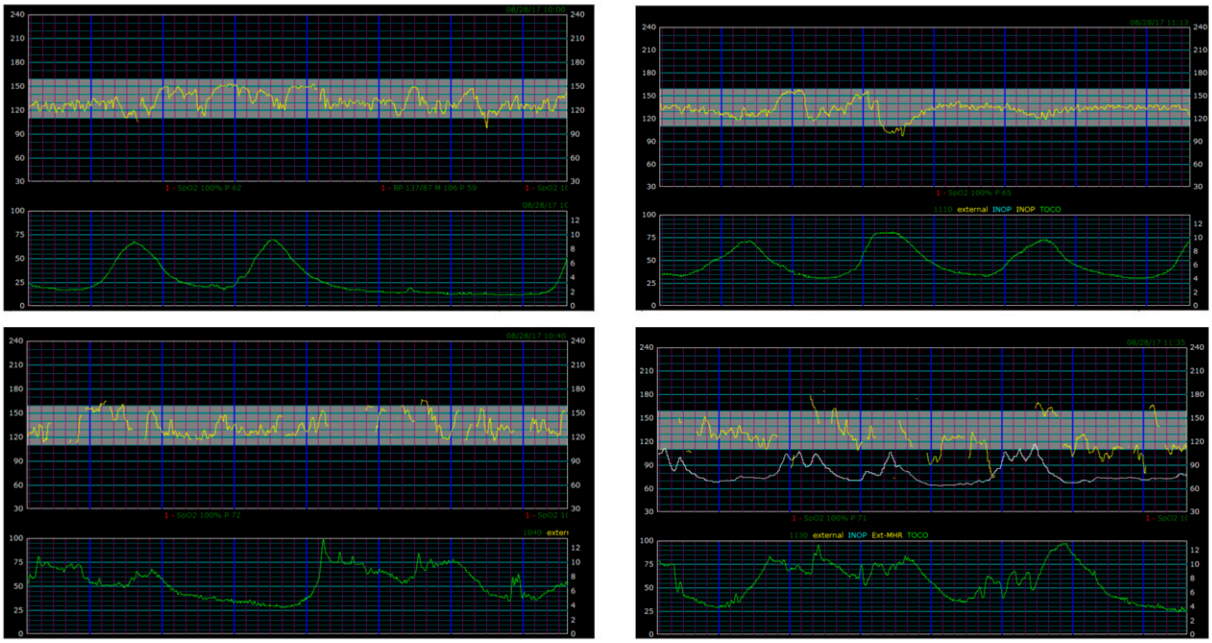

Figure 7. Electronic fetal monitoring strip 7.

Our patient received antenatal corticosteroids at a gestational age beyond 34 weeks. Current guidelines recommend administration of antenatal corticosteroids in steroid-naïve women during the late preterm period, defined as 34 0/0 to 36 5/7 weeks of gestation, if she is at high risk for preterm birth within the next 7 days. (5) Because the current patient was nulliparous and demonstrated cervical change to 3 cm, it was not known whether she would progress in her labor. Therefore, there was perceived benefit of giving her corticosteroids to decrease the neonatal risk of respiratory distress syndrome. The study of pregnant women with a history of bariatric surgery reported that late preterm infants had a relative risk of 0.80 (95% confidence interval, 0.66–0.97) for adverse respiratory outcome in the betamethasone group compared with the placebo. (6) We theorize that the intervention of betamethasone may have decreased the risk of respiratory morbidity in this fetus with marked variability.

Teaching points for this case:

1. Marked variability of the FHR tracing may be associated with respiratory morbidity; however, data regarding its significance are limited.
2. Recognizing the reassuring aspects of a category II FHR tracing prevented a preterm delivery.

Prior bariatric surgery in a pregnant woman warrants evaluation for nutritional deficiencies and anemia that may be undiagnosed.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the significance, interpretation, and management of abnormalities or changes in fetal heart rate patterns during labor including reassuring and nonreassuring and indeterminate patterns.

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ANSWER KEY FOR JANUARY 2018 NEOREVIEWS

Coagulation Disorders in the Newborn: 1. E; 2. B; 3. C; 4. A; 5. C.

Placental Transfusion: Current Practices and Future Directions: 1. B; 2. D; 3. B; 4. B; 5. C.

Strip of the Month: Marked Variability: To Worry or Not?

Diana S. Wolfe and Kafui A. Demasio

NeoReviews 2018;19;e53
DOI: 10.1542/neo.19-1-e53

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Vernix Caseosa–like Hyperkeratotic Plaques in a French Canadian Infant

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THE CASE

A male infant was born at 34 weeks' gestation with generalized hyperkeratotic plaques on the limbs along with extensive areas of vernix caseosa–like changes on the head and trunk.

Prenatal and Birth Histories

- 32-year-old gravida 1, para 1 woman with a normal fetal survey
- Pregnancy was complicated by mild polyhydramnios; premature rupture of membranes occurred at 32 weeks' gestation
- First child of nonconsanguineous parents of French Canadian ancestry
- Estimated gestational age was 34 weeks
- Spontaneous vaginal delivery of male infant following unstoppable preterm labor; prophylactic antibiotics were started when the membranes ruptured 2 weeks earlier; Apgar scores were 7 and 8 at 1 and 5 minutes, respectively; no resuscitation required
- Birthweight 2.415 kg (50%), birth head circumference 32.5 cm (90%), birth length 44 cm (50%)

Presentation (Day of Birth)

At birth, striking skin changes were noted in the form of generalized edematous spongy hyperkeratotic plaques on the limbs along with extensive areas of vernix caseosa–like changes on the head and trunk (Fig 1). The amniotic fluid appeared thickened because of the presence of skin debris. The infant did not have any respiratory distress. The infant was placed in an incubator with 60% to 70% humidity.

Physical Examination (Day of Birth)

- Vital signs: All in normal range
- Skin: Diffuse hyperkeratotic plaques over trunk and extremities, as shown in Fig 1
- Head: Normocephalic; normal fontanelles; symmetric facies
- Oral cavity: Normal mucosae, intact palate, no lymphadenopathy
- Lungs: Clear, equal breath sounds; no respiratory distress
- Cardiovascular: Normal S1, S2; regular rate and rhythm; no murmurs or gallops
- Abdomen: Normal, soft, no organomegaly
- Genitourinary: Normal male genitalia; patent anus
- Skeletal: Spine appears normal
- Neurologic: Symmetric Moro reflex, normal strength and tone

AUTHOR DISCLOSURE Drs Al-Musalhi, Lovett, Srolovitz, Jahnsen, Schlipf, Fischer, and Khnykin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

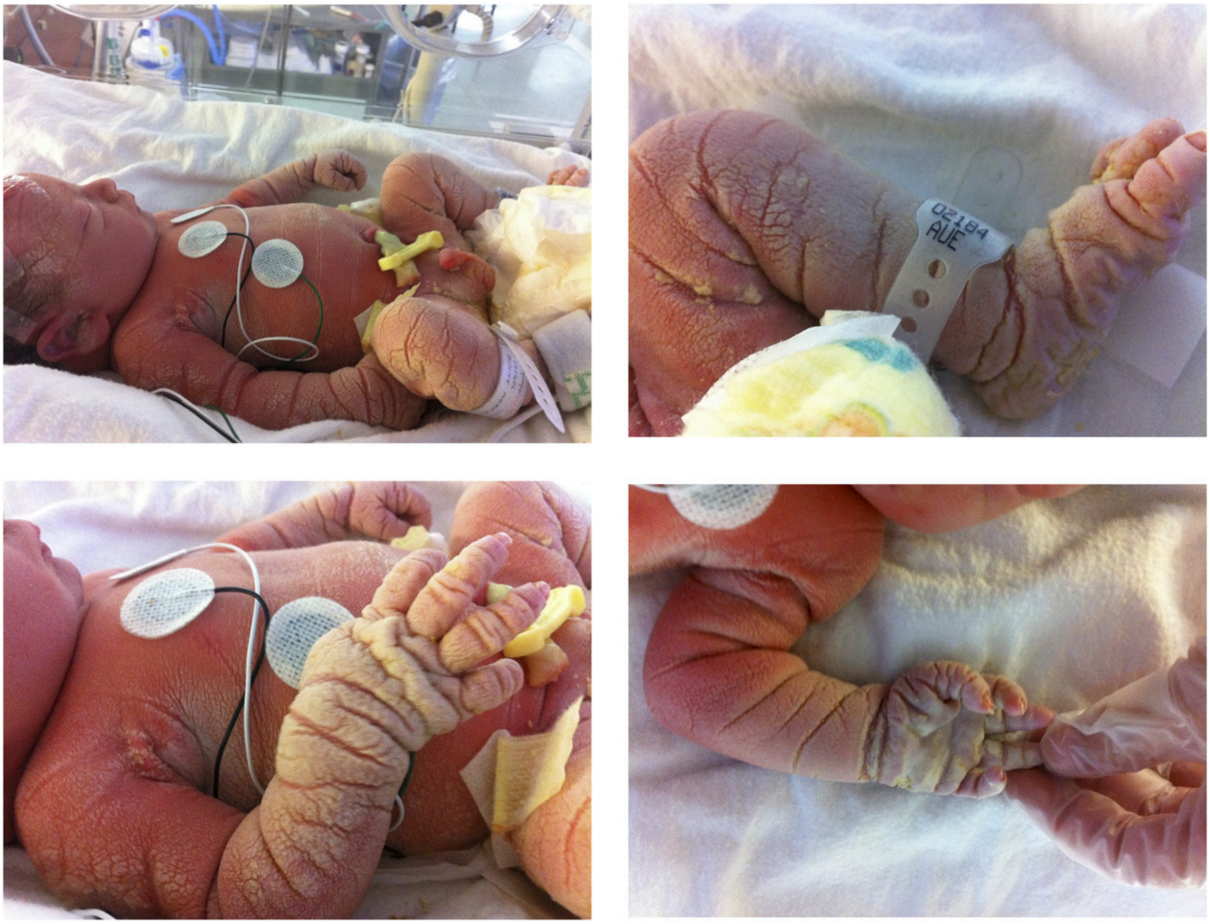

Figure 1. Generalized verrucous hyperkeratosis and vernix caseosa–like changes.

Laboratory Studies

- White blood cell count: 17,500/μL (17.5×10^9/L) with 41% neutrophils, 34% lymphocytes, and 13% eosinophils
- Hemoglobin: 14.1 g/dL (141 g/L)
- Platelet count: $215\times10^3/\mu$L (215×10^9/L)
- Blood culture was sent

Progression

Skin abnormalities improved dramatically during the first few weeks after birth with liberal application of petroleum jelly (Fig 2). The infant passed the hearing screening. A skin biopsy was performed with light and electron microscopy analyses that showed hyperkeratosis, acanthosis, follicular

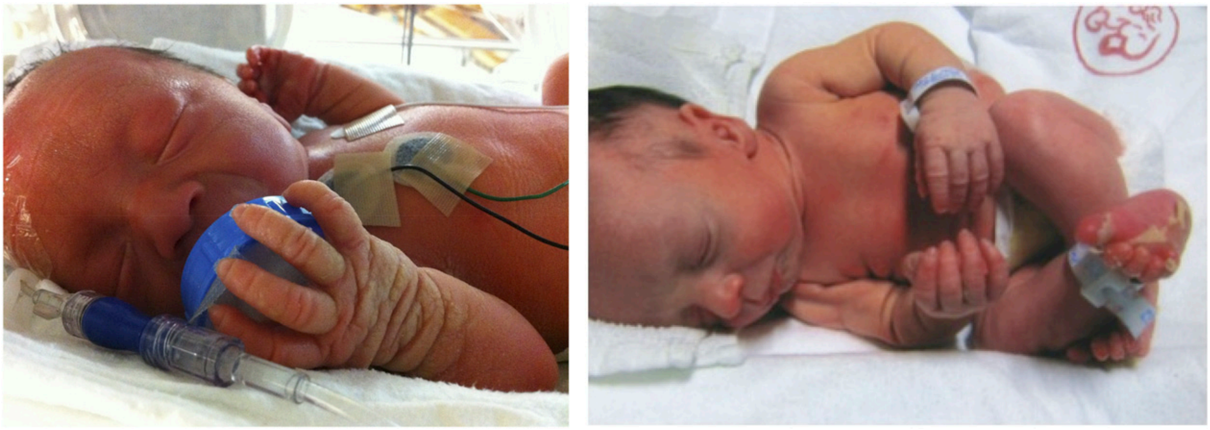

Figure 2. A few weeks after birth, remarkable improvement was noted in the hyperkeratosis.

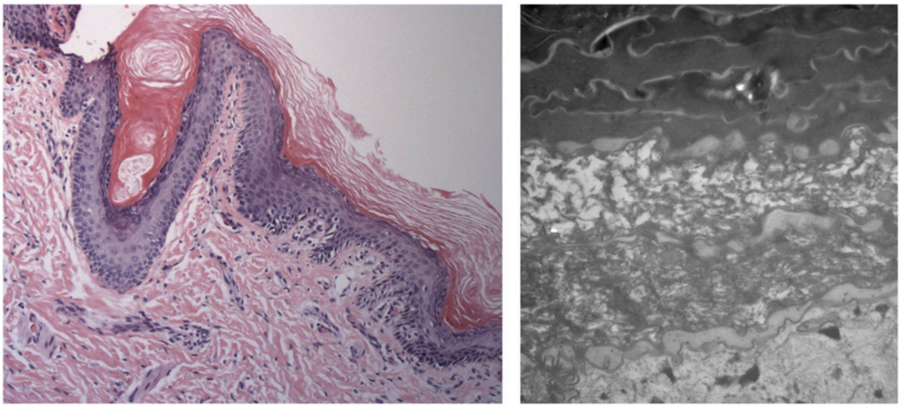

Figure 3. Skin biopsy light and electron microscopy showed hyperkeratosis, acanthosis, follicular plugging, and curved lamellar structures in the upper epidermis.

plugging, and curved lamellar structures in the upper epidermis (Fig 3).

DIFFERENTIAL DIAGNOSIS

- Extensive generalized hyperkeratotic plaques in a preterm infant
- Epidermolytic ichthyosis
- Harlequin ichthyosis
- Ichthyosis prematurity syndrome (IPS)
- Keratitis-icthyosis-deafness (KID) syndrome
- Lamellar ichthyosis (LI)
- X-linked ichthyosis

ACTUAL DIAGNOSIS: ICHTHYOSIS PREMATURITY SYNDROME

The family history revealed a case of unspecified congenital ichthyosis in the mother's second-degree cousin. IPS was suspected clinically and the diagnosis was confirmed with genetic testing. Mutation analysis in the *FATP4* gene (*SLC27A4*, OMIM*604194, chromosome 9q34.11) was performed using polymerase chain reaction followed by DNA sequencing. The analysis detected 2 heterozygous DNA changes c.418G>A (p.V140M) and c.861_862dupCC (p.L288PfsX20) in the *FATP4* gene in this patient. The mother is a carrier of the heterozygous 2–base pair duplication c.861_862dupCC (p.L288PfsX20) in exon 6. To our knowledge, these 2 mutations (c.418G>A, p.V140M and c.861_862dupCC, p.L288PfsX20) have not been previously described in patients with IPS.

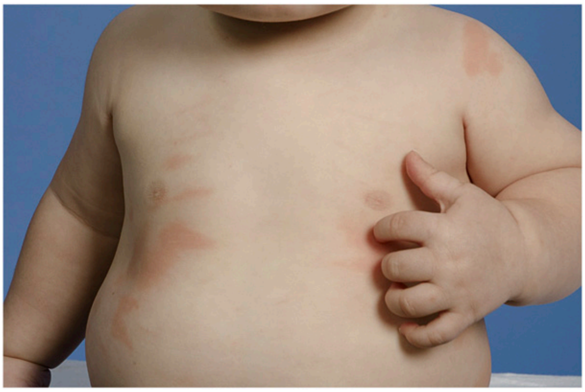

Figure 4. Marked dermatographism with minor friction.

During follow-up at the age of 10 months, the child presented with mild ichthyosis and atopic manifestations in addition to marked dermatographism with minor friction (Fig 4). These findings were managed with emollients.

WHAT THE EXPERTS SAY

IPS is a rare, heterogeneous, autosomal recessive, congenital ichthyosis characterized by preterm birth (typically 30–32 weeks' gestation), perinatal depression, thick vernix caseosa–like desquamating epidermis, and transient eosinophilia. (1) In IPS, the pregnancy is frequently complicated by polyhydramnios and characteristic ultrasonographic features, such as separation of the chorionic and amniotic membranes, echogenic amniotic fluid, and echo-free chorionic fluid described as having a starry-sky appearance. (2) Polyhydramnios is a universal feature of IPS that can be explained by the presence of thick epidermal debris in the stomach, which impedes the passage of the amniotic fluid through the gastrointestinal system. (3)

Perinatal depression is a complication of this condition that probably results from aspiration of thick amniotic skin debris. (2) After surviving the critical neonatal period, the thick caseosalike epidermis desquamates, and patients manifest a lifelong nonscaly ichthyosis with atopic features and dermatographism. (4) The pathognomonic feature of electron microscopy analysis of skin biopsy specimens is the trilamellar membrane aggregations in the stratum corneum and stratum granulosum. (1)(5)

The initial clinical skin findings in this neonate appear to fit within the spectrum of autosomal recessive congenital ichthyoses, which include LI, congenital ichthyosiform erythroderma (CIE), and harlequin ichthyosis. However, different morphologic aspects usually characterize these conditions at birth. LI and CIE typically manifest with a collodion membrane, which is a tight translucent shiny cast encasing the newborn. Harlequin ichthyosis is suspected when the infant is covered with a thick armorlike cast leading to extreme ectropion and eclabium; this disorder is associated with high perinatal mortality risk. After shedding these 2 types of membranes, infants affected by these conditions typically present with varying degrees of ichthyosis with generalized scale. This differs from IPS in which the skin is relatively normal in appearance after the membrane is shed.

The characteristic vernix caseosa–like scale seen in IPS has not been described in LI, CIE, or harlequin ichthyosis but can be observed in keratitis-icthyosis-deafness (KID) syndrome. KID syndrome is characterized by generalized or focally accented hyperkeratosis with palmoplantar involvement along with specific extracutaneous findings such as keratitis and variable degree of bilateral sensorineural hearing loss, which was not found in this case. Also, prematurity and neonatal respiratory distress are not features of KID syndrome.

The scales in X-linked ichthyosis are fine and superficial, and are not usually present at birth but develop shortly after birth with no scalp involvement; the scales then fade within weeks and recur as a clear generalized dark ichthyosis with sparing of body folds later in life. The other distant possibility in the differential diagnosis in this case is epidermolytic ichthyosis (bullous congenital ichthyosiform erythroderma), which is characterized at birth by erythroderma with widespread skin blistering that evolves into a hyperkeratotic ichthyosis, most pronounced on flexures with only minimal focal blisters.

IPS was suspected in this case because of the clinical presentation of thick, caseous, desquamating epidermis and preterm birth. Although this infant did not have perinatal depression, the pregnancy was complicated by polyhydramnios, a known feature of IPS. The diagnosis was confirmed by ultrastructural analysis of a skin biopsy specimen with electron microscopy and by the mutation analysis of the *FATP4* gene.

IPS was recently shown to be caused by mutations in the *FATP4* gene (*SLC27A4* /OMIM * 604194), which is important for lipid homeostasis and skin barrier formation. (6) This gene expresses a transmembrane protein that transports exogenous fatty acids into cells and also functions as an acyl coenzyme A synthetase, activating long and very long-chain fatty acids for subsequent intracellular metabolism. (7) The function of *FATP4* gene is very important in maintaining fatty acid metabolism for normal epidermal barrier function. (6) A mouse model deficient for this gene showed disturbed epidermal barrier function and waxy thickened restrictive skin. (8)

IPS has been reported frequently in Norway and Sweden (9) and a few isolated cases have been reported in Germany, (10) France, (11) North Africa, (6) and the Middle East. (6) To our knowledge, this is the first case reported in a French Canadian family; these 2 compound heterozygous mutations in the *FATP4* gene have not been reported previously.

In conclusion, IPS is a rare form of syndromic ichthyosis, which is characterized by distinct clinical features in the prenatal and postnatal periods, typical ultrastructural skin abnormalities, and defined genetic mutations. IPS may be more prevalent than previously recognized because cases have been identified in different parts of the world. Identifying this syndrome is essential to provide optimal perinatal care and reassure parents and pediatricians about its benign course beyond the perinatal period.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Demonstrate understanding of inheritance patterns and recurrence risks for autosomal recessive disorders.
- Know how to recognize, diagnose, and manage scaly disorders of the skin, including neonatal ichthyoses.

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Vernix Caseosa–like Hyperkeratotic Plaques in a French Canadian Infant

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- Joseph Hageman, MD, owns stocks and bonds and is on the advisory board of Owlet, Inc.
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- Josef Neu, MD, has disclosed he has research grants and serves on the Scientific Advisory Boards of Medela and Infant Bacterial Therapeutics, and that he serves on the scientific advisory board of Nutricia.

Answer Key appears on page e126.

Evidence for Role of Genital Mycoplasmas in Preterm Birth and Neonatal Lung Injury

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Education Gaps

1. Although *Ureaplasma* respiratory colonization is a risk factor for bronchopulmonary dysplasia, there is a gap in knowledge concerning the impact on longer-term respiratory outcomes.
2. It remains to be determined in sufficiently powered randomized clinical trials whether eradication of ureaplasmas from the intra-amniotic cavity antenatally or the respiratory tract postnatally prevents preterm birth or ameliorates its short- or long-term complications.

Abstract

Although the genital mycoplasmas are common commensals in the vaginal flora of up to 80% of women, these organisms have been associated with adverse perinatal outcomes. These outcomes include chorioamnionitis, preterm premature rupture of the membranes (pPROM), preterm birth, and altered lung development contributing to the development of bronchopulmonary dysplasia in preterm infants with respiratory infection. This review focuses on the current knowledge of the evidence supporting a causal role of these organisms in these adverse outcomes and controversies, including whether treatment of affected pregnant women or their infants is warranted.

Objectives

After completing this article, readers should be able to:

1. Discuss the role of genital mycoplasmas in the pathogenesis of preterm birth and neonatal lung injury that contributes to bronchopulmonary dysplasia.
2. Review the clinical presentation of ureaplasmal respiratory infection.
3. Discuss the diagnostic evaluation for suspected ureaplasmal infection.
4. Discuss the potential treatment options and status of clinical trials of antibiotic treatment to prevent adverse respiratory outcomes in preterm infants with *Ureaplasma* species respiratory infection.

AUTHOR DISCLOSURE Dr Viscardi has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

BPD	bronchopulmonary dysplasia
PCR	polymerase chain reaction
pPROM	preterm premature rupture of membranes

INTRODUCTION

The genital mycoplasmas are bacteria included in the phylum Tenericutes, class Mollicutes, that are characterized by their small genome size, lack of a cell wall, limited biosynthetic capabilities, resistance to ß-lactam antibiotics, and specific growth requirements. (1) There are 16 Mollicute species that have been isolated from humans, of which 6 species are considered pathogens: *Mycoplasma pneumoniae, Mycoplasma fermentans, Mycoplasma hominis, Mycoplasma genitalium, Ureaplasma parvum,* and *Ureaplasma urealyticum*. This review will focus on the species that have been linked to complications during pregnancy and adverse neonatal outcomes (2)(3) (Table 1). It will summarize the current evidence for a pathogenic role of these organisms, the clinical presentation in the neonate, and diagnostic methods, and the controversy about treatment of these organisms is reviewed.

Pathogenic Genital Mycoplasmas

M hominis. *M hominis* may be detected in the vagina or cervix in 20% to 50% of sexually active women in the presence or absence of *Ureaplasma* species (1); organism numbers increase in the presence of bacterial vaginosis. (3) In addition to bacterial vaginosis, *M hominis* is associated with 1) maternal conditions such as pyelonephritis, pelvic inflammatory disease, chorioamnionitis, early miscarriages, midtrimester abortions, and postpartum endometritis; and 2) neonatal conditions including congenital pneumonia, meningitis, and bacteremia. (1)(4) Genome sequencing of *M hominis* isolates from infected amniotic fluid and placentas identified a microbial gene of unknown function that was associated with bacterial burden in amniotic fluid and risk for preterm delivery in women with preterm labor. (5) These results suggest that *M hominis* strains vary in their pathogenic potential and the development of screening methods for molecular detection of virulence genes may identify therapeutic targets as well as identify women at highest risk for preterm birth. Although vertical transmission of *M hominis* occurs, neonatal respiratory colonization rates are 5% to 10% and the association with bronchopulmonary dysplasia (BPD) is less established than with the more common *Ureaplasma* species. (6)

These organisms metabolize arginine as an energy source, and colonies may be identified in culture on agar medium by their characteristic fried egg appearance. *M hominis* expresses a variable adherence antigen that may assist organisms to evade the host immune response by varying the size and phase of the surface antigen. The *M hominis* genome contains 665 kb with 527 protein-encoding genes, making it the second smallest known self-replicating, free-living organism. (3)

M genitalium. *M genitalium* is a significant cause of male urethritis, female cervicitis, and pelvic inflammatory disease. (3) It is much less common than *M hominis* or the *Ureaplasma* species, with detection in the vagina or cervix of 0% to 5% of women. The organisms attach to and invade epithelial cells by a terminal structure, the MgPa adhesion. Antigenic variation of the adhesion protein is a host immune response evasion mechanism. The 580-kb *M genitalium* genome is the smallest of free-living organisms with only 485 protein-encoding genes. Because it is difficult to perform cultures of *M genitalium*, molecular assays are most commonly used for detection. (1)

***Ureaplasma* Species.** The *Mycoplasma* species *U parvum* (serovars 1, 3, 6, and 14) and *U urealyticum* (serovars 2, 4, 5, and 7-13) are the most common organisms detected in infected amniotic fluid and infected placentas with or without other organisms in extremely preterm (7) and late preterm/term

TABLE 1. **Characteristics of Human Genital *Mycoplasma* Species**

SPECIES	MORPHOLOGY	GENOME SIZE	METABOLIC SUBSTRATES	VAGINAL COLONIZATION	DISEASE ASSOCIATION
Ureaplasma parvum/Ureaplasma urealyticum	7-15 μm colonies Agar	*U parvum*: 750 kb *U urealyticum*: 947 kb, 27%–30% GC content	Urea	40%–80%	Urethritis, CAM, postpartum endometritis, PB, BPD, meningitis
Mycoplasma hominis	200 μm colonies, "fried-egg" appearance	665 kb, 27% GC content	Arginine	20%–50%	PID, BV, CAM, congenital pneumonia, meningitis
Mycoplasma genitalium	Difficult to cultivate; PCR for detection	580 kb; 32% GC content	Glucose	0–5%	Urethritis, cervicitis, PID

BPD=bronchopulmonary dysplasia; BV=bacterial vaginosis; CAM=chorioamnionitis; GC=guanine-cytosine; PB=preterm birth; PCR=polymerase chain reaction; PID=pelvic inflammatory disease.

pregnancies (8) with chorioamnionitis. These species are associated with spontaneous preterm birth. (2) *U parvum* is the predominant species in clinical specimens from amniotic fluid, cord blood, neonatal respiratory secretions, and cerebrospinal fluid (9) but evidence for differences in serovar-specific virulence is currently lacking. However, evidence from epidemiologic studies and experimental infection models has demonstrated that these organisms contribute to complications of preterm birth including BPD, (9)(10) necrotizing enterocolitis, (11)(12) and central nervous system injury/inflammation (meningitis, intraventricular hemorrhage). (12)(13) The following sections review the evidence implicating ureaplasmas in the pathogenesis of chorioamnionitis, preterm birth, and neonatal lung injury.

***Ureaplasma* Species and Chorioamnionitis.** Intrauterine infection and inflammation are common antecedents of spontaneous preterm birth. (14) *Ureaplasma* species can be detected as early as the time of genetic amniocentesis at 15 to 17 weeks' gestation in up to 11% of pregnancies. (15) Although not all women infected with *Ureaplasma* species experience chorioamnionitis or preterm delivery, the time from amniocentesis to delivery was shorter when *Ureaplasma* species were detected in the amniotic fluid than in cases where *Ureaplasma* species were absent. (16) In a study of the vaginal microbiome, *Mycoplasma* and/or *Ureaplasma* were detected using polymerase chain reaction (PCR) in 81% (29/36) of women with preterm premature rupture of membranes (pPROM), and presence of these organisms was associated with lower gestational age at delivery. (17)

Experimental *U parvum* intra-amniotic inoculation established a chronic infection with evidence of inflammation in amniotic fluid, placenta, and fetal tissues in both sheep and Rhesus macaques, but only induced preterm labor in the nonhuman primate Rhesus model. (18) Recently, Lal et al (19) demonstrated that *U parvum* serovar 3 and *U urealyticum* serovar 10 express the serine protease prolyl endopeptidase and induce neutrophil matrix metallopeptidase 9, which together stimulate fetal membrane collagen fragmentation, resulting in the release of the neutrophil chemoattractant tripeptide proline-glycine-proline. This microbial-host interaction may explain, in part, how ureaplasmas contribute to both pPROM and chorioamnionitis. Thus, perinatal infections with *Ureaplasma* species are an important cause of pPROM and preterm labor and delivery. These data also demonstrate the difficulties of reversing *Ureaplasma*-induced pathologies with postnatal treatment because many preterm infants may have been exposed to these organisms antenatally, often for prolonged durations.

Respiratory Infection in Preterm Newborns

Ureaplasmas can be transmitted to the fetus/newborn respiratory tract by vertical transmission at the time of birth, via an ascending infection through direct contact with infected amniotic fluid, or possibly a hematogenous route. (9) Detection of *Ureaplasma* species with culture and/or PCR in nasopharyngeal or tracheal aspirates is inversely related to gestational age, with the overall incidence being 35% among infants with birthweights less than 1,501 g. (10) Although most studies focused on colonization in the first 7 to 10 days of age, serial sampling suggests that the infection persists for weeks in many infants. The host and organism factors that determine persistent infection versus transient colonization are unknown.

Culture-independent studies of the lung microbiome have confirmed that the lower airways are not sterile, as previously believed. Although studies of the newborn lung microbiome are technically challenging in infants receiving mechanical ventilation, recent studies have confirmed the presence of *Ureaplasma* species in the context of the microbial community and relationship to BPD. Lal et al (20) observed that the lung microbiome was similar at birth in extremely low-birthweight infants and term infants. The predominant phyla on the first day after birth in both extremely low-birthweight and term infants were Firmicutes, Proteobacteria, Actinobacteria, Bacteroidetes, Tenericutes *(Ureaplasma)*, *Fusobacterium*, Cyanobacteria, and Verrucomicrobia. In established BPD, the phylum Proteobacteria was increased, and phyla Firmicutes and Fusobacteria were decreased. In an analysis of lung microbiome characteristics in association with BPD severity, the infants who developed severe BPD exhibited greater bacterial community turnover with age, less abundant *Staphylococcus* in the first week after birth, and higher initial relative abundance of *Ureaplasma*. (21)

Both host and microbial factors determine the susceptibility of preterm infants to *Ureaplasma* species respiratory tract colonization and persistence of infection. Critical host factors include developmental deficiencies and genetic mutations in innate immune defenses. The preterm lung is deficient in surfactant protein A, which is required for ureaplasmal phagocytosis, killing in vitro (22) and pathogen clearance, and modulating the inflammatory response in vivo. (23) Single nucleotide polymorphisms in relevant Toll-like receptors may affect both the susceptibility to *Ureaplasma* respiratory infection and the risk of developing BPD in infected preterm infants. (24) Ureaplasmas possess multiple host immune response avoidance mechanisms that facilitate establishing a chronic infection in the amniotic cavity and the neonatal respiratory tract. These include 1) phase and size variation of the multiple banded antigen, (1) 2) the ability to form biofilms, (25) 3) presence of multiple nucleases that may degrade neutrophil extracellular traps formed when activated neutrophils release granule proteins and chromatin that kill bacteria, (26) and 4) downregulation of various endogenous antimicrobial peptides. (27)

Respiratory tract colonization is associated with a proinflammatory response in the lung that is augmented by volutrauma and oxygen exposure. (9) The effects of intra-amniotic exposure to *U urealyticum* 2 days before delivery and subsequent mechanical ventilation for 14 days were assessed in a 125-day preterm baboon model of BPD. Preterm baboons exposed in utero to *Ureaplasma* with persistent postnatal ureaplasmal infection had higher tracheal aspirate inflammatory cytokines at birth and at 14 days of age, and more severe BPD changes, including extensive fibrosis compared with intra-amniotic exposed animals in which the infection cleared, and noninfected controls. (18) Transforming growth factor $ß_1$ was elevated in tracheal aspirates of infants who progressed to BPD and was increased in autopsy lung specimens from *Ureaplasma*-infected preterm infants (28)(29) and in the infected preterm baboon model. Upregulation of transforming growth factor $ß_1$ signaling during lung development as a result of inflammation contributes to alveolarization arrest, airway remodeling, and fibrosis, all of which are characteristic of BPD. (9)

Ureaplasma Respiratory Colonization as an Independent Risk Factor for BPD

As a result of improvements in neonatal care, BPD is now a disease limited to the most immature infants, and is seen in 30% of infants born at 28 weeks' gestation or earlier. (30) The "new" BPD (characterized by more uniform inflation, fewer but larger alveoli, and less severe, but persistent inflammation) results from interruption of normal developmental signaling during the saccular stage of lung development. This injury is often initiated in utero by an intrauterine infection and a subsequent dysregulated inflammatory response. (30)

Three meta-analyses of more than 40 studies over the past 30 years have confirmed that *Ureaplasma* respiratory colonization is an independent risk factor for BPD. (10)(31)(32) In the most recent meta-analysis in 2014, *Ureaplasma* respiratory tract colonization led to a 3-fold higher risk for BPD at 28 days and 2-fold higher risk at 36 weeks' postmenstrual age. (9)(10) Remarkably, this association has remained unchanged over the past 3 decades, despite many changes in neonatal care.

CLINICAL MANIFESTATIONS IN INFANTS

Infants with *Ureaplasma* respiratory colonization are more likely born extremely preterm to women with pregnancies complicated by chorioamnionitis and preterm labor or pPROM (33)(34) (Table 2). The vertical transmission rate increases with longer duration of membrane rupture, (35) while infants delivered for maternal indications have the lowest rate of respiratory tract colonization. (36) Interestingly, infants with *Ureaplasma* respiratory colonization may present with a peripheral blood leukocytosis, (37) but exhibit mild respiratory distress syndrome (33) that evolves rapidly in the first 2 weeks of age into early BPD with radiographically evident emphysematous changes and histologic early fibrosis and disordered elastin. (29)(38)

TABLE 2. **Characteristic Clinical and Laboratory Findings in *Ureaplasma*-Positive Preterm Infants***

CLINICAL PRESENTATION	LABORATORY/RADIOGRAPHIC FINDINGS
POL or pPROM	Bistratified inflammatory pattern chorioamnionitis
GA<28 weeks	Leukocytosis at birth
Mild RDS, but worsening gas exchange requiring increased respiratory support in 2nd week after birth	Early radiographic emphysematous changes

GA=gestational age, POL=preterm onset of labor, pPROM=preterm premature rupture of membranes; RDS respiratory distress syndrome.
**Used with permission from Viscardi, RM. Pre and postnatal microbial colonization and respiratory outcomes in preterm infants. In: Bancalari E, ed.* The Newborn Lung: Neonatology Questions and Controversies. *2nd ed. Philadelphia, PA: WB Saunders/Mosby/Churchill Livingstone/Butterworth-Heinemann/Hanley & Belfus; 2012. (39)*

Diagnosis

Laboratory detection of *Ureaplasma* species in neonates can be achieved on culture or using molecular methods such as the PCR assay in tracheal and nasopharyngeal aspirates, pleural fluid, lung tissue obtained at autopsy, urine, blood, or cerebrospinal fluid. (40) Because ureaplasmas are extremely sensitive to adverse environmental conditions, particularly dessication and heat, specimens should be inoculated directly into appropriate transport media such as 10B broth or universal transport media for mycoplasmas, ureaplasmas, and chlamydiae available from various commercial suppliers. The specimens should then be placed on ice or refrigerated if immediate transportation to the laboratory is not possible. If a specimen must be shipped and/or if the storage time is likely to exceed 24 hours before it is processed, the specimen in transport medium should be frozen at −80°C to prevent loss of viability and to minimize bacterial overgrowth.

Growth of ureaplasmas in vitro requires a complex medium containing serum, growth factors such as yeast extract, and urea as a metabolic substrate. Serially diluted specimens should be inoculated into 10B broth and subcultured directly onto A8 agar. Broths should be incubated at 37°C under atmospheric conditions while agar plates should be incubated in room air supplemented with 5% to 10% carbon dioxide for at least 7 days. An alkaline color change from yellow to pink in 10B broth as a result of urea hydrolysis is most likely attributable to *Ureaplasma* species, but *M hominis* may coexist with *Ureaplasma* in clinical specimens. Brown granular colonies 10 to 60 μm in diameter visualized on A8 agar under a stereomicroscope after 24 to 48 hours of incubation are diagnostic of *Ureaplasma* species. MYCOSCREEN PLUS and MYCOFAST US (Wescor Inc, Logan, UT) are commercial kits available for detection and quantitation of *Ureaplasma* species and *M hominis* based on the color change of specific wells containing substrates and inhibitors. PCR assays may be performed to distinguish *U parvum* from *U urealyticum,* but identification to the species level is not necessary for clinical diagnostic purposes. Details of various nucleic acid amplification tests and their applications for detection of mycoplasmas and ureaplasmas have been discussed in depth in a recent review. (1) Antimicrobial susceptibility testing for ureaplasmas of clinical isolates to macrolides, tetracyclines, and fluoroquinolones can be performed by broth microdilution, (41) but is not routinely performed because resistance to macrolides, the agents of choice for use in most neonatal infections, is uncommon and such testing is available in only a few specialized reference laboratories.

Treatment

Current Status of Recommendations for Treatment of *Ureaplasma* Infection in Preterm Infants. Trials of antibiotic therapy with erythromycin in the first few weeks of age often failed to eradicate respiratory colonization and had no impact on the development of BPD in *Ureaplasma*-infected infants. (9) Recent retrospective studies demonstrated that azithromycin treatment failed to improve outcomes when initiated after 2 weeks of age in symptomatic, culture-proven *Ureaplasma*-positive infants. (42)(43)

Azithromycin in Preterm Infants. Previous studies may have failed to show microbiologic efficacy in part because of lack of preliminary pharmacokinetic/pharmacodynamic studies of erythromycin and azithromycin in the preterm population to determine effective dosage. We have focused on the azalide azithromycin because its immunomodulatory properties make it an ideal candidate for therapy to prevent *Ureaplasma*-mediated lung injury in preterm infants. We conducted pharmacokinetic/pharmacodynamic studies characterizing the population pharmacokinetics, safety, tolerability, and microbiologic effects of 10 and 20 mg/kg intravenous single-dose azithromycin and 20 mg/kg every 24 hours for 3 days multiple dose in preterm neonates born at 24 to 28 weeks' gestation who are at high risk for *Ureaplasma* respiratory tract colonization and BPD. (44)(45)(46) The disposition of azithromycin in plasma was biphasic, suggesting that the antibiotic's pharmacokinetics follow a 2-compartment model. Compared with the single-dose groups, the 20 mg/kg multidose effectively eradicated *Ureaplasma* in all subjects who were colonized before the dose. The short course azithromycin regimen appeared safe, with no deaths or serious adverse events attributed to the drug. Azithromycin has been associated with increased risk for cardiovascular death in older adults, due to its proarrhythmic potential, (47) and infantile hypertrophic pyloric stenosis in infants. (48) Therefore it cannot be recommended for routine use in preterm infants with suspected *Ureaplasma* infection until further randomized trials confirm its safety and efficacy.

Other macrolides may be beneficial in the treatment of *Ureaplasma* respiratory colonization. In a placebo-controlled trial of a 10-day course of 20 mg/kg per day clarithromycin, there was a 68.5% eradication rate 2 days after the last dose in treated colonized infants. In addition, the BPD rate was greatly reduced in treated colonized infants compared with the placebo group (3% vs 36%). (49) However, this study had several limitations: it excluded infants smaller than 750 g who have the highest *Ureaplasma* colonization rate and risk for BPD; the duration of mechanical ventilation was brief in all subjects; culture status was based solely on nasopharyngeal cultures so it did not differentiate between upper and lower respiratory tract infection; and organism clearance was not assessed in the placebo group. Although there have been case reports of torsades de pointes in adults treated with clarithromycin, (50) the risk of idiopathic hypertrophic pyloric stenosis with clarithromycin is unknown. Therefore, data on the safety and efficacy are insufficient to recommend the use of clarithromycin for improving pulmonary outcomes in *Ureaplasma*-infected preterm infants.

SUMMARY

Epidemiologic and experimental evidence has been accumulating to support a causal role of the genital mycoplasmas, particularly *Ureaplasma* species, in subclinical intrauterine infections. Such infections contribute to chorioamnionitis, pPROM, and preterm birth, and neonatal morbidities including neonatal lung injury. Future research should use comprehensive "omic" approaches to identify host and microbial factors that identify pregnancies at risk for preterm birth. Clinical trials are needed to address whether maternal and/or neonatal therapy targeting *Ureaplasma* infection is safe and effective in eradicating the organisms and preventing adverse consequences.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, pathogenesis, and prevention of perinatal infection with *Mycoplasma* and *Ureaplasma*.
- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infection with *Mycoplasma* and *Ureaplasma*.

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1. A 24-year-old gravida 1, para 0 woman presents at 24 weeks 3 days of gestation with preterm premature rupture of membranes (pPROM). If amniocentesis were to be performed, which of the following mycoplasma species would be MOST likely to be detected in the amniotic fluid?

   A. *Mycoplasma hominis.*
   B. *Ureaplasma urealyticum.*
   C. *Mycoplasma genitalium.*
   D. *Ureaplasma parvum.*
   E. *Mycoplasma pneumonia.*

2. The woman undergoes further evaluation and treatment. It is known that genital mycoplasmas are common commensals of the vaginal flora and have been associated with adverse pregnancy outcomes. Which of the following statements about the pathogenic role of these organisms during pregnancy is TRUE?

   A. *Mycoplasma hominis* is strongly associated with pPROM in primiparous women.
   B. *Ureaplasma parvum and Ureaplasma urealyticum* (*Ureaplasma* species) are an important cause of chorioamnionitis but not pPROM or preterm labor.
   C. *Mycoplasma genitalium* is associated with bacterial vaginosis and preterm labor.
   D. *Ureaplasma* species is usually detected as early as 10 to 12 weeks of gestation in the amniotic fluid.
   E. *Mycoplasma* and/or *Ureaplasma* are detected in up to 81% of women with pPROM, and their presence is associated with lower gestational age at delivery.

3. The woman is admitted to the hospital for latency antibiotics and observation. She develops a fever 5 days into her hospital stay and is diagnosed with chorioamnionitis. Which of the following placental pathology results BEST describes the characteristic findings seen in *Ureaplasma* species infection?

   A. Placental destruction with callous trophoblast cell apoptosis.
   B. Necrotizing funisitis with chronic villitis.
   C. Bistratified inflammatory pattern.
   D. Chronic villitis with Hoffbauer cells.
   E. Villous inflammation and sclerosis with trophoblastic necrosis.

4. *Ureaplasma* colonization of the respiratory tree has been shown to be an independent risk factor for bronchopulmonary dysplasia (BPD). Which of the following statements is CORRECT regarding *Ureaplasma* respiratory colonization and risk for BPD?

   A. Transforming growth factor ß$_1$, which contributes to alveolarization arrest, airway remodeling, and fibrosis, is increased in autopsy lung specimens from *Ureaplasma*-infected preterm infants.
   B. In the most recent meta-analysis in 2014, *Ureaplasma* respiratory tract colonization increased the risk for BPD at 36 weeks' postmenstrual age by 4-fold.
   C. Respiratory tract microbiome studies indicate that infants who developed severe BPD have a higher abundance of *Staphylococcus* in the first week after birth and lower initial relative abundance of *Ureaplasma.*
   D. Treatment with azithromycin has been shown to improve the outcome of BPD at 28 days.
   E. When it occurs in the presence of other early-onset bacterial infections, *Ureaplasma* respiratory colonization is associated with a decreased likelihood of development of BPD.

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5. Because of the history and presentation, you decide to evaluate the infant for *Ureaplasma* infection. Which of the following statements is CORRECT regarding the laboratory detection of *Ureaplasma* species?

   A. Tracheal and nasopharyngeal aspirates are the only biological samples in which *Ureaplasma* species can be detected in the preterm neonate.
   B. Brown granular colonies 10 to 60 μm in diameter visualized on A8 agar under a stereomicroscope after 24 to 48 hours of incubation are diagnostic of *Ureaplasma* species.
   C. Because of their robust resistance to adverse environmental conditions, specimens can be kept on the specimen retrieval device and kept in room temperature for up to 48 hours before laboratory evaluation.
   D. Growth of *Ureaplasma* in vitro is generally quick and results in positive culture detection within 48 hours in most cases.
   E. An alkaline color change from yellow to pink in 10B broth is indicative of *Mycoplasma hominis*, but not *Ureaplasma* species.

Evidence for Role of Genital Mycoplasmas in Preterm Birth and Neonatal Lung Injury

Rose M. Viscardi

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A Focus on Microbiome Completeness and Optimized Colonization Resistance in Neonatology

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Education Gaps

1. The potential for microbiome-based complementary therapies when antibiotics are required is not fully realized.
2. Colonization resistance can be a tool for minimizing health risks during the neonatal period.

Abstract

The human microbiome contributes a majority of genes and significant metabolic capacity to the newborn. The infant's bacteria, archaea, viruses, and fungi are also critical for immune maturation and neurologic development. Because a microbiota is highly malleable, it is an ideal target for improving infant health. Yet, management of this major biological resource to reduce health risk for the infant has been comparatively neglected to date. This review discusses the opportunities for a more holistic, ecological approach to infant health with an emphasis on the microbiome, which includes 1) the benefits of microbiome completeness (microbial seeding and feeding), as well as 2) optimized colonization resistance. The latter can better protect against infectious as well as noncommunicable diseases by shifting pathogen load requirements for producing disease, protecting mucosal barriers, and optimizing immune homeostasis.

Objectives

After completing this article, readers should be able to:

1. Discuss the neonatal microbiome and its impact on infant and later-life health.
2. Consider mutualistic and commensal microbiota and their regulation of barrier (eg, gut, skin, lung, urogenital) function and immune maturation.
3. Use colonization resistance as a primary infectious disease prevention strategy.
4. Discuss commonalities between noncommunicable and communicable diseases with a focus on barrier function and immune maturation.

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ABBREVIATIONS

CR	colonization resistance
HMOs	human milk oligosaccharides
NCDs	noncommunicable diseases and conditions

INTRODUCTION

Study of the human microbiome, the trillions of microbial organisms and their genes found in humans, is revolutionizing our preventive and therapeutic approaches to human health. (1) Modern medicine is gradually transiting from a mid-20th century paradigm in which the healthiest infant was thought to be one largely free of microbes to a new era in which increasing numbers of obstetricians/gynecologists, neonatologists, and pediatricians understand that an infant must be heavily microbially laden to develop into a healthy child. This microbial requirement for health and well-being is not exclusive to humans but is a fundamental characteristic of most plants, insects, and animals on earth. (2)(3)

Humans are not a single-species mammal and should no longer be medically treated as such. Instead, we are a holobiont or superorganism with both microbial and human eukaryotic cells and genes. In fact, by most estimates, the human body is mostly composed of microbes (based on the number of both cells and genes). In many ways, we are most analogous to a coral reef or a tropical rain forest, each of which contains myriad species and is healthiest when all of the species are present, cooperating, and, themselves healthy. The collection of human microbiota (organisms composed of bacteria, archaea, viruses, fungi) residing on and in the infant, along with their genes, represents the infant's microbiome. Different species of microbes have different environmental requirements (eg, nutrients, oxygen levels) for growth, and those able to thrive in the colon are not the same as the ones adapted to the mouth or skin.

The challenge for obstetricians/gynecologists, neonatologists, and pediatricians is to fully embrace the new role, that of microbial managers, which is an inherent part of supporting the health of the human holobiont. The first 1,000 days after birth have been recognized as a critical developmental window during which the neonatal microbiome sets the template for subsequent development. (4) For this reason, medical management of the microbiome takes on added importance in the newborn and infant. An ecological management approach to the newborn and infant microbiome can reduce the risk of not only conditions such as obesity, diabetes, and inflammatory diseases, but also the risk of life-threatening infections. This review will describe how the microbiome becomes an integral part of the infant and why proactive management of the infant microbiome is a critical factor for both childhood and adult health. An emphasis will be placed on the perinatal microbiome and risk reduction for infectious diseases through a microbial process known as *colonization resistance* (CR). (5)

THE MATERNAL MICROBIOME AND PREGNANCY OUTCOMES

Pregnancy and birth are the greatest environmental and microbial transitions that an infant will face across life. During this time, the infant emerges from the protected environment of the womb to the world of environmental challenges including the battle against pathogens capable of producing life-threatening infectious diseases. Planning for a healthy, microbially complete infant begins with the pregnant woman. This is because her microbiome composition determines her donation of a majority of cells and genes to the infant. If the maternal microbiome has been compromised through associated diseases and conditions (eg, obesity, diabetes), dysbiosis-producing infections, environmental factors (eg, urban-associated pollutants, processed foods), or drug treatments (eg, antibiotics), the infant will begin life with a degraded, dysbiotic microbiome. When the pregnant woman's microbiome has been previously compromised, even efficient seeding of the newborn, as occurs with vaginal delivery, can increase neonatal health risks because of impaired adaptive perinatal immune development. (6) Interrupting the cycle of disease epidemics by ensuring a healthy infant microbiome should be a major health goal along with developing microbial-based strategies to address what is increasingly becoming an intergenerational problem. (7)

Exposure to microbes begins early in life because the placenta carries its own microbiome. (8) Recent studies are examining whether any seeding of an infant's gut occurs prenatally. (9) Beyond the effects of the placental microbiome, the maternal microbiome appears to affect the course of the pregnancy. Composition of the microbiome, including both biomass and diversity, in various maternal body sites (oral, vaginal, gut, cervical, placental) can drive the course of the pregnancy, affecting such factors as risk of preterm delivery. (10)

Newborns literally become filled with trillions of bacteria, viruses, archaea, and fungi during the developmental period surrounding birth. The acquisition of these microbes in newborns (largely from the mother and surrounding environment) is both necessary and required for normal physiologic development and function. (4)(11)(12)

The infant microbiome takes up residence in numerous body sites including the skin, but barrier-protected mucosal tissues (eg, gut, respiratory, urogenital tract) are particularly rich in microbiota. Not surprisingly, these body sites are where the infant is exposed to the external environment, and also, where a majority of immune cells reside. (13) The traditional routes of external environment (inhalation, oral, and dermal exposures) are rich repositories of microbiota. Because of this, the infant's microbiota serves as both a gatekeeper and a filter for the infant's experience with the external environment including exposure to environmental chemicals, drugs, food, food additives, and pathogens. (14) The infant's internal body (effectively the internal doses) only sees these chemical and microbial factors after the microbiome has interacted with and acted on them.

INFANT METABOLISM OF FOOD AND DRUGS

From the standpoint of risk-benefit, it is impossible to know precisely how much nutrient, drug, active drug metabolite, or environmental chemicals will reach a given patient's cells and tissues without knowing the status of the microbiome and its metabolic contributions. This uncertainty arises because the composition of the microbiota (eg, bacterial species, strains, communities, and genes) determines how chemicals and drugs are handled. This is both bad news and good news.

The bad news is that, in the absence of information on an infant's microbiome, physicians may be flying blind when administering drug therapies to patients. (15) Different microbes carry different genes and have different metabolic capabilities. (16) These can affect the delivered dose of many prescribed drugs including 5-fluorocytosine, digoxin, indomethacin, insulin, ketoprofen, loperamide oxide, methotrexate, metronidazole, nitrazepam, nizatidine, olsalazine, paracetamol, prontosil, and sulfasalazine. (15)(17)(18)(19) Because of the wide range of enzyme activities within the human microbiome and the extensive variation in microbiome status among patients, the delivered internal dose of an active drug can be very imprecise in the absence of a patient's microbiome profile. Take, for example, the case of β-glucuronidase activity within the microbiome. Glucuronidases are enzymes that can convert certain prodrugs to active compounds, and in other cases, remove potentially toxic drug metabolites. Hence, glucuronidase activity within a patient can affect both deposition and concentration. (20) A recent atlas of β-glucuronidase activity within the human intestinal microbiome reflects the extent to which the microbiome determines the outcome of administered drugs. In addition, comprehensive approaches to predicting microbiome-driven drug metabolism is under way. (21) The human gut microbiome has more than 3,000 drug-metabolizing glucuronidase enzymes, with more than 100 unique to the microbiome to understand the extent of the problem. The good news is that future drug therapies will be working by tapping the microbiome as a way to produce useful "internal drugs." (22)

COMATURATION OF MICROBES AND PHYSIOLOGIC SYSTEMS

One of the most significant changes in our paradigm of 21st century human biology and medicine is the recognition that our mutualistic and commensal microbes shape, if not direct, the infant's physiologic development and function. (23)(24) Physiologic systems such as immune, neurologic, endocrine, and gastrointestinal are undergoing benchmark developmental changes during the perinatal period, and these critical developmental changes can affect lifelong health. In particular, the immune system must quickly adapt from a pregnancy-skewed environment in which certain immune response capacities (eg, Th1 responses) are dampened versus the postnatal world where discernment of pathogenic threats and the capacity to mount a more complete repertoire of host defenses is needed. The perinatal period of development is arguably the most significant window of development affecting the health, not only of the child, but also of the later-life adult. In the absence of an adequate microbiome, the immune system is imbalanced and deficient in certain specialized populations. For example, in the extreme case of germ-free mice, there is significant underdevelopment of the specialized gut mucosal tissues such as the Peyer patches, lymphoid follicles, and mesenteric lymph nodes. (25)

Postnatal immune development is critically dependent on various interactions with mutualistic and commensal microbes, and immune dysfunction–mediated disease is an expected outcome of an inadequate microbiome. (26)(27) Infants with depleted microbiomes, such as occurs after exposure to antibiotics, are biologically and functionally incomplete. Because the microbiome has been described functionally as representing a new endocrine organ, a second brain, and a second liver, (2) incompleteness of the newborn's microbiome is functionally analogous to a birth defect, though in this case, it is a preventable birth defect. (28)(29)

Even minor alterations in the early-life comaturation of an infant's microbiome and immune system can have significant health consequences. As reviewed by Amenyogbe et al, (30) microbial and immune homeostasis in the infant are completely interconnected, with the former temporally preceding the latter during early development. For example, infants with increased fungal species *Rhodotorula* and *Candida* and reduced levels of *Bifidobacterium*, *Lactobacillus*, and *Akkermansia* bacteria were at increased risk for atopy and also possessed a gut environment that overpromoted interleukin-4 production, an immunoglobulin E–promoting cytokine. In contrast, the presence of specific bacterial species in newborns such as *Bacteroides fragilis* appears to dampen both immune inflammatory cell signaling and the production of inflammatory cytokines in the infant. (30) *B fragilis* is also important for altering the balance of 2 critical populations of immune regulatory cells: natural T-regulatory cells and invariant natural killer T cells. The former are increased while the latter are decreased in the intestine when the bacterium is sufficiently present in early life. (30) The Figure illustrates T-regulatory cells as an important immune population that needs to become established in the infant.

Entire fields of study are devoted to the developmental origins of adult health and disease and for good reason. (31) Interruption of key developmental events can epigenetically and physiologically program the child for a life course filled with health issues. (32) Various factors can affect microbiome seeding, feeding, and homeostasis, including mode of delivery, intrapartum and infant antibiotics, maternal diet, maternal and infant probiotics, and infant feeding (eg, extent and duration of breastfeeding).

Because of the 1,000-day critical window for the human microbiome, (4) clinicians working in neonatology are in a unique position to support proper childhood physiologic development. But not just any collection of microbiota will suffice when it comes to adequate support of immune, neuronal, respiratory, and endocrine development and establishment of a healthy pathway for later life.

HEALTH CONSEQUENCES OF MICROBIAL INCOMPLETENESS (DYSBIOSIS)

Noncommunicable Diseases and Conditions

Considerable research has gone into the associations between microbiome imbalances and the risk of both noncommunicable diseases and conditions (NCDs) and communicable (ie, infectious) diseases. Disruption of the infant microbiome

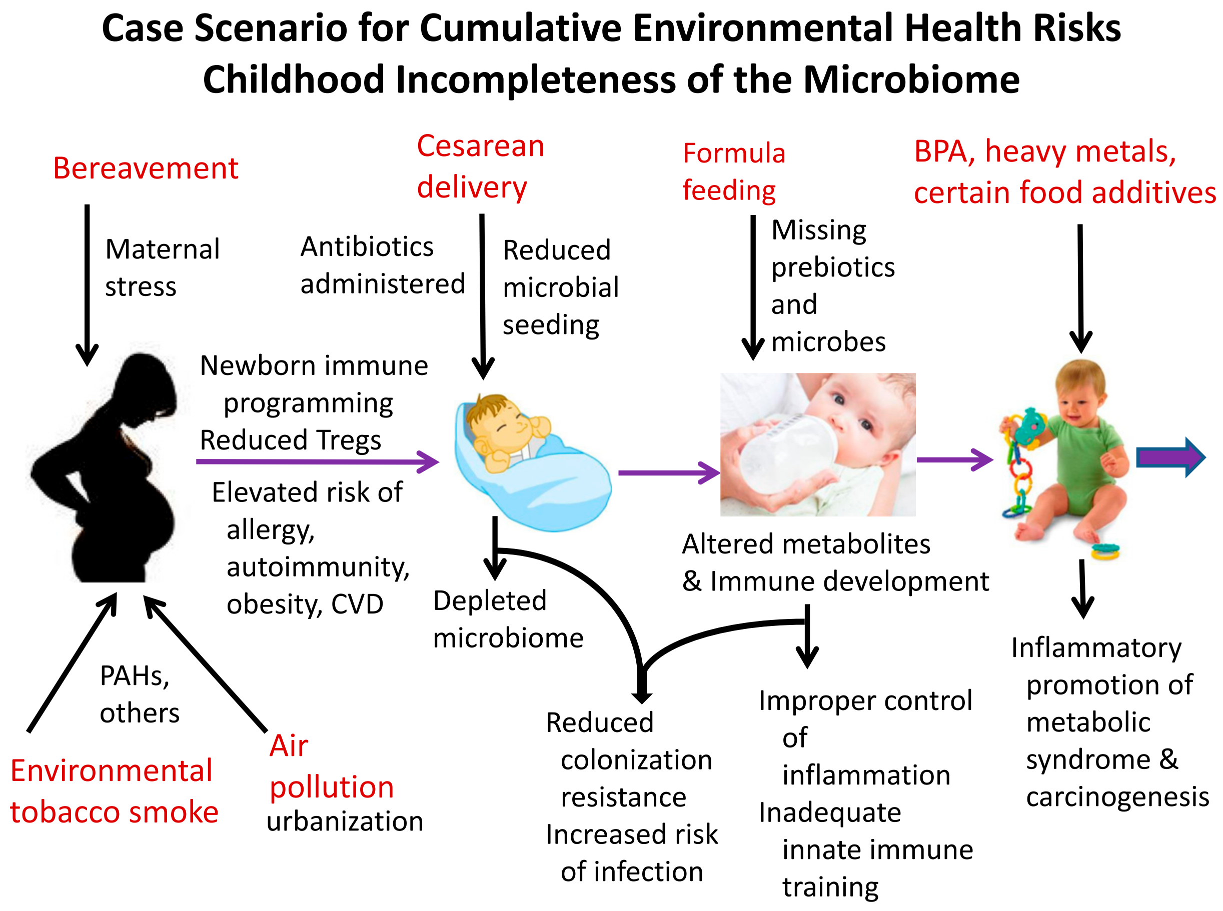
Case Scenario for Cumulative Environmental Health Risks
Childhood Incompleteness of the Microbiome
Bereavement
Maternal stress
Cesarean delivery
Antibiotics administered
Reduced microbial seeding
Formula feeding
Missing prebiotics and microbes
BPA, heavy metals, certain food additives
Newborn immune programming
Reduced Tregs
Elevated risk of allergy, autoimmunity, obesity, CVD
Depleted microbiome
Altered metabolites & Immune development
PAHs, others
Environmental tobacco smoke
Air pollution
urbanization
Reduced colonization resistance
Increased risk of infection
Improper control of inflammation
Inadequate innate immune training
Inflammatory promotion of metabolic syndrome & carcinogenesis

Figure. A timeline of environmental factors that affect the microbiome from pregnancy through infancy is illustrated. Cumulative factors are shown that can adversely affect 1) infant microbiota status/level of microbiome completeness, 2) immune development, 3) regulation of inflammation, 4) the level of colonization resistance, and 5) the risk of both noncommunicable and infectious disease. Maternal microbial status, infant microbial seeding and feeding, and risk of exposure to microbially toxic drugs, chemicals, foods, and food additives all contribute to the overall risk for the child. BPA=bisphenol A; CVD=cardiovascular disease; PAH=polycyclic aromatic hydrocarbons; Treg=T-regulatory cells.

elevates the risk of both childhood- and adult-onset NCDs (eg, obesity, asthma, diabetes, cardiovascular disease, cancer, autoimmune conditions) as well as the contribution of microbiome degradation to the ongoing NCD epidemic. (2) In some cases, cause-effect relationships are unknown between changes in microbiota and changes in risk of disease. However, in other cases, there is significant mechanistic information detailing precisely how changes in gut microbiota, cellular signaling, and microbial metabolism drive changes in the risk of disease (supported by shifts in host barrier function, physiology, mucosal immune status, and inflammation-driven tissue pathology.) For example, evidence of a causal relationship between microbiome dysbiosis and specific diseases include the observation in mice that Crohn disease–like ileitis is fully transmissible. Transplantation of the dysbiotic gut microbiota results in the failure of protective Paneth cell function and production of disease. (33) But the risk of a dysbiotic microbiome resulting in NCDs is frequently delayed when compared with the more immediate danger of infant infectious diseases.

A pivotal factor in the relationship between microbiome degradation and elevated risk of disease is the fact that not every species of bacteria is equal in importance. Certain bacteria are redundant in that multiple species can carry out overlapping functions, and the presence of any 1 of these species may be sufficient to meet our needs. In contrast, several functionally unique bacterial species, termed *keystone species*, carry out critical biological and/or metabolic functions that are not duplicated elsewhere across the microbiome. When keystone species are lost due to drug, chemical, dietary, psychosocial, or other environmental damage, pathology is likely. (2)

Infectious Diseases

If the path from microbiota to NCDs is often lengthy and potentially delayed in emergence, gaps in microbiome communities and their functions can give pathogens a straightforward and rapid foothold. Both microbiota and our immune cells are significantly enriched at mucosal barriers. These barriers developed to separate us from the external environment and its threats and a wide range of pathogens that gain access to the host via these mucosal barriers. (34) Therefore, the status of host defenses at these barriers is a significant factor in vulnerability to infections. At the center of infant risk of infectious diseases are 3 primary superorganism-based factors: 1) status of the developing immune system as conditioned largely by the microbiota, 2) integrity of the mucosal barrier itself, and 3) CR, or mechanisms to protect against the incursion of and/or overgrowth of pathogens.

Infant immune development begins with the maternal diet and microbiome (24) and continues to be shaped postnatally during critical windows of development. (2) Mucosal barrier integrity is greatly affected by microbiome homeostasis, which affects both mucin regulation and thickness as well as immune signaling and control of inflammation. (35) CR includes not only the capacity of commensal and mutualistic microbes to physically exclude access of pathogens to mucosal surfaces, but also the capacity of the infant microbiome to create cooperation among microbes against pathogens as well as metabolically deficient or antagonistic local environments that deter pathogens.

As discussed by Hand, (36) all infectious diseases are contextual, and are based on combinations of interactions that involve microbes, the host, and the environment. However, most considerations of infectious diseases start and stop with the invading pathogenic organism. Only recently have we realized that it is the microbial ecology of our barriers and immune-microbe interactions that are the tipping point when it comes to risk of infectious diseases. However, to fully engage this broader view of infectious disease ecology, it is necessary to focus on the neonatal microbiome. For example, commensal and mutualistic microbes have extensive cross-talk with the immune system, and in combination, help the host to shape the production of specific antimicrobial peptides at mucosal barriers. These, in turn, also shape microbiota composition, resulting in immune development, and risk of infection. (37) The Figure illustrates examples of factors, conditions, and medical interventions during pregnancy and early childhood that cumulatively contribute to microbiome damage, altered immune development in the infant, and elevated risk of both infectious diseases and NCDs.

ANTIBIOTICS AND THE INFANT MICROBIOME

While antibiotics may be necessary to treat both maternal and infant bacterial infections, unintended damage to the infant microbiome from antibiotics can present a serious problem if no complementary therapy such as probiotic and/or prebiotic is used. Antibiotics may be necessary to eliminate life-threatening bacterial infections, but overuse of antibiotics remains a concern. (38) For example, in a recent cohort survey among 5,581 children in New Zealand, 97% of the children had received at least 1 course of antibiotics by age 5 years. These children were prescribed 53,052 courses of antibiotics. (39)

Recently, the oral microbiome is emerging as a sentinel for antibiotic interruption of maternal-infant microbiota.

The earliest oral microbiome in the infant tends to mirror that of the mother. However, because antibiotics are often administered prophylactically during cesarean delivery as a preventive measure against possible postsurgical infections, (40) disruption of the microbiome can occur before birth. Gomez-Arango et al (41) studied 36 mother-infant pairs comparing mother-newborn oral microbes and the impact of intrapartum antibiotic administration. They found that the infant's oral microbiome most resembled the oral microbiome of the mother. However, the colonizing bacteria were shaped by the maternal exposure to the antibiotic, producing the following 2 key effects: 1) Antibiotic resistance genes were enriched in the infant's oral microbiome of those with antibiotic-treated mothers. 2) The colonizing microbes were skewed toward a hospital-rich, inflammation-producing bacterial profile (eg, Proteobacteria families such as Bradyrhizobiaceae, Sphingomonadaceae, Comamonadaceae, Neisseriaceae, and Oxalobacteriaceae) with a concomitant reduction in those bacteria (Streptococcaceae, Gemellaceae, and the Lactobacillales order) needed to promote a healthy progression of infant microbes as the infant matures.

CR AND PATHOGEN LOADING

Mutualistic and commensal microbes in the gut provide CR against both endogenous and exogenous pathogens. In a recent review, Kim et al (5) detailed 6 mechanisms of CR in the gut that can reduce the risk of pathogen-induced disease. Three direct routes of CR include 1) the capacity of the gut mutualistic and commensal microbiota to deplete the local environment of key nutrients required by the pathogen, 2) the ability of some microbiota to produce bacteriocins (toxic peptides) that act against specific pathogens, and 3) the use of type VI secretion systems by some gram-negative bacteria that result in membrane-associated, cell-cell toxicity against competing pathogens. Three indirect mechanisms of CR also reduced the risk of infectious disease and include 1) receptor-mediated stimulation of innate immune cells to produce antimicrobial peptides against pathogens, 2) metabolism of bile acids to produce metabolites that are toxic for certain pathogens, and 3) maintenance of the mucin layer and protection of the gut barrier by ensuring that epithelial cells are not damaged by pathogens.

The level of CR present in the infant gut can affect the minimum number of pathogenic organisms required to produce disease. Increasing the level of CR also increases the minimum load of pathogens required in the individual to bypass host defenses and produce disease. For this reason, optimizing CR through proactive management of the infant microbiome is a useful preventive strategy. There are key opportunities to institute this approach.

Microbial completeness (establishment of key founding species and richness of microbiota) at birth and microbial feeding and nurturing with human milk oligosaccharides are important steps in shifting the minimal pathogenic load needed to produce disease. But rather than requiring thousands of specific bacterial species to become established in locations such as the gut, there is evidence that gene- and metabolism-directed microbial seeding with a handful of bacterial species may be sufficient for effective CR against significant human pathogens. For example, using microbial loading of germ-free mice to examine resistance against the human enteric pathogen *Salmonella enterica* serovar Typhimurium, Brugiroux et al (42) reported that as few as 15 bacterial strains afforded the same level of protection against *Salmonella* infection as did a complete robust microbiome. Even more importantly, the bacterial genome design was used to determine the minimum number of friendly bacteria needed to provide protection.

Both probiotics and prebiotics have the capacity to shift the level of CR. For example, human breast milk contributes not only immune components such as immunoglobulin A to the infant, but also maternally derived microbiota (a natural form of probiotics). (43)(44) Human milk oligosaccharides (HMOs) are the natural component of breast milk that aid the growth and maturation of useful gut bacteria that can compete against pathogens. In addition, HMOs can also directly inhibit the growth of group B *Streptococcus* in a manner that is independent of their effect on host immunity. (45) The HMOs seem to function as an alternate substrate for group B enzyme activity, which results in reduced growth capacity of the bacterium. As such, HMOs can provide direct antimicrobial activity for these pathogens. In a separate study of group B *Streptococcus*, both growth and biofilm formation were inhibited by HMOs. (46)

INFANT SELF-COMPLETION FOR HEALTH RISK REDUCTION

NCDs and communicable (infectious) diseases have historically been viewed as completely distinct, with the latter being horizontally transmissible via the transfer of disease-producing microbes. However, emerging fundamental characteristics of the human microbiome are beginning to challenge the idea that NCDs and communicable diseases are necessarily completely separate and distinct. In a recent *Lancet Global Health* editorial, the authors argued that NCDs share social factors and are, in effect, socially transmitted conditions. (47) Unlike communicable diseases, which follow the 4 criteria of disease transmissibility based on the Koch postulates, (2) NCDs have been considered to be nontransmissible via the horizontal or vertical transfer of specific microbes (eg, viruses, bacteria, fungi, parasites). But social conditions (diet, lifestyle, air and water pollutants, built environments, elective cesarean deliveries, formula feeding), in part, can shape a human's microbial composition (most of the cells and genes of the microbiome.)

If a dysbiotic microbiome can produce disease, and microbiome elements of the dysbiosis can be transferred vertically (via the pregnant woman) and even horizontally (such as among household members), then there may be a communicable component to the risk of NCDs. The concept is that during periods in which an individual's microbiome has been degraded (eg, after treatment with antibiotics) and CR is low, acquisition of microbiota from human-human contact and the local environment could predispose the recipient to misregulated inflammation and future NCDs.

Some evidence supports this theory. First, microbiota can be readily horizontally transferred when recipients are depleted in their microbiome diversity. This transfer can occur not only among members of the same species, but also between some species. Howler monkeys fed a highly restrictive diet in US zoos lost microbiome diversity over time. The microbiota of their closest contacts (human zoo handlers) became established in these animals, thereby "humanizing" the microbiomes of the captive animals. (48) Such transfers have the capacity to transfer microbiota-induced physiologic changes that predispose individuals to specific NCDs. Researchers recently transferred the capacity for atopic dermatitis in mice via the transfer of specific gut microbiota. (49) Similarly, Crohn disease–like ileitis can be transferred among mice by transferring dysbiotic, but not healthy, gut microbiota. (33)

Sharing of microbes between the mother and newborn and among household members is not restricted to pathogens. Mutualistic and commensal microbes also can be shared among household members and their pets (eg, dogs). Humans crowded into built environments and detached from the rich diversity of environmental/agrarian microbes will encounter narrow, passively accumulated and largely skin-derived microbiota as they move within the urban landscape. (50) In effect, urban-dwelling humans are more likely to share human-derived microbes that have been tailored by the very social factors that promote microbial dysbiosis and NCDs.

CONCLUSIONS

Active ecological management of the perinatal and infant microbiome offers significant opportunities to reduce health risks not only in the infant but also across later life. Most human genes and key metabolic pathways are present in the microbiota, which are concentrated around both mucosal tissues (eg, the gastrointestinal tract and airways) and additional portals of the infant's exposure to the external environment (eg, skin). Microbiome assessment should be an annual part of patient personalized medical evaluation. Maternal diet, drugs, environment (eg, urbanization), stress, and birth delivery mode all affect the newborn's microbial composition. Breastfeeding further benefits microbial seeding, feeding, and maturation of the infant microbiome as well as physiologic maturation. Microbial gene- and metabolism-directed optimization of the microbiome via diet, prebiotics, and probiotics—particularly during the first 1,000 days—can aid CR against pathogens. Pathogens not only produce infectious disease, but also can damage barrier function, and predispose the immune system toward inflammation-driven NCDs. For this reason, there is benefit in including optimized CR as a disease management and prevention goal within neonatology. Drug-induced damage to CR should be addressed with complementary therapies to restore this function.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- For antibiotics used commonly in the neonate, know indications for their use, clinical effects, pharmacokinetics, side effects, and toxicity.

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1. While making rounds in the NICU, you encounter a patient who is receiving antibiotics and several other medications. As you consider how the microbiome may affect the actions of those medications, which of the following enzymes can be found in the infant microbiome that could convert certain prodrugs to active compounds and in other cases, remove potentially toxic drug metabolites?
    - A. Lysosomal lipase.
    - B. β-Glucuronidase.
    - C. Coenzyme Q.
    - D. Bacterial ribonuclease.
    - E. Super-β-phosphocarboxymase.
2. A family has a history of atopy, including eczema and asthma, in their children. For a newborn in this family, increased levels of which of the following may increase the risk of atopic disease?
    - A. *Bifidobacterium.*
    - B. *Lactobacillus.*
    - C. Fungal species *Rhodotorula* and *Candida.*
    - D. *Bacteroides fragilis.*
    - E. Natural T-regulatory cells.
3. While discussing the use of antibiotics in protocols to prevent early-onset sepsis, a colleague mentions that changing practices may alter the presence of keystone species. Which of the following is an appropriate characterization of keystone species?
    - A. Mammals in which widespread increase in antibiotic therapies have led to a significant increase in somatic growth both prenatally and postnatally.
    - B. A group of viruses that provide enteric enzymes that aid in human digestion.
    - C. Functionally unique bacterial species that carry out critical biological or metabolic functions that are not duplicated across the microbiome.
    - D. Bacteria and mammal species that work together living in close physical association to the advantage of both.
    - E. Bacteria that rely on key nutrients and hormones provided by the host organism to proliferate.
4. A pregnant woman at term gestation enters the labor and delivery department, and the fetus is in breech presentation. A cesarean delivery is planned and the woman receives antibiotics for surgical prophylaxis. Which of the following statements regarding maternal receipt of antibiotics and the neonatal microbiome is correct?
    - A. There is a higher likelihood of antibiotic-resistant genes being enriched in the infant’s oral microbiome.
    - B. The neonatal microbiome will have increased growth of Streptococcaceae and Lactobacillales.
    - C. The neonatal microbiome will shift to resembling more of the father’s profile than the mother’s.
    - D. Colonizing microbes in the infant will have a deficiency of Proteobacteria compared with the mother.
    - E. The timing of antibiotics so close to the time of delivery will ensure that there will be zero impact on the neonatal microbiome.
5. You are counseling a family regarding the benefits of breastfeeding. They are aware of the potential immune benefit, but ask about other potential benefits. Which of the following statements concerning breastfeeding, immune function, and microbial completeness is correct?

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A. The most abundant immunoglobulin found in human milk is immunoglobulin E.
B. Human milk oligosaccharides aid growth and maturation of useful gut bacteria, and can inhibit growth of group B *Streptococcus*.
C. Human milk is the most sterile fluid in the human body, because it contains multiple antimicrobial agents and properties.
D. The most recent evidence points to the key feature of microbial completeness being thousands or millions of specific bacterial species to be established in the gut to "compete" with each other to prevent neonatal disease.
E. Neisseriaceae, Comamonadaceae, and Oxalobacteriaceae are increasingly recognized as the key bacteria that promote healthy progression of a stable neonatal microbiome that prevents infectious disease.

A Focus on Microbiome Completeness and Optimized Colonization Resistance in Neonatology

Rodney R. Dietert

NeoReviews 2018;19;e78
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Neonatal Herpes Simplex Virus Infection

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Education Gaps

1. Neonatal herpes simplex virus is a virus capable of infecting the central nervous system of neonates, causing significant morbidity and mortality.
2. Neonatal herpes simplex virus should be considered as a possible etiologic factor when a neonate presents with signs of sepsis.

Abstract

Herpes simplex virus (HSV) is among the most severely debilitating viruses that can infect the neonate, and is associated with significant mortality and morbidity. Neonatal HSV infection generally is acquired in the peripartum period, and can be devastating if not diagnosed appropriately. Studies conducted over several decades have advanced our knowledge of the benefit of antiviral therapy on neonatal HSV disease outcomes. As such, many neonates now are effectively treated and experience no or fewer long-term sequelae of this potentially devastating infection. Clinicians must be astute, because early diagnosis and early treatment are key to a better prognosis.

Objectives

After completing this article, readers should be able to:

1. Discuss the timing and risk factors for neonatal infection.
2. Review the clinical manifestation of neonatal infection and disease.
3. Discuss the diagnostic evaluation of neonatal herpes simplex virus (HSV) disease.
4. Identify the treatment of neonatal HSV.
5. Identify the outcomes of neonatal HSV treatment.

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ABBREVIATIONS

ANC	absolute neutrophil count
CNS	central nervous system
CSF	cerebrospinal fluid
HSV	herpes simplex virus
PCR	polymerase chain reaction
SEM	skin, eyes, and mouth

INTRODUCTION

Numerous viruses are capable of infecting the central nervous system (CNS) of neonates, but herpes simplex virus (HSV) is among the most severe, with significant mortality and morbidity. Unlike other viral pathogens, HSV is treatable using a commercially available antiviral drug, acyclovir. Neonatal HSV infection is primarily acquired during the peripartum period, which improves the likelihood that antiviral therapy can be beneficial. Viral damage is of a relatively short duration in neonatal HSV disease acquired at birth compared with injury to the developing fetal brain from viruses that are acquired in utero. Studies conducted by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group over the course of 4 decades have advanced our knowledge of the favorable impact that antiviral therapy has on neonatal HSV disease outcomes. Many neonates now are effectively treated and experience no long-term sequelae of this potentially devastating infection. Without treatment, however, neonatal HSV disease can be fatal and extremely devastating. It is important for clinicians and healthcare professionals to recognize signs of neonatal HSV infection. This can lead to prompt diagnosis and treatment, leading to a better prognosis for infants affected by the virus.

EPIDEMIOLOGY

The HSV consists of enveloped, double-stranded DNA. (1) The virus establishes latency after a primary infection, and then periodically reactivates and causes recurrent symptomatic disease. It can also cause asymptomatic viral shedding that is clinically unapparent. The incidence of neonatal HSV infection is between 1 in 3,000 and 1 in 20,000 live births. (1) Recent data suggest that this disease incidence may be increasing. (2) Neonatal HSV is acquired in 1 of 3 distinct periods: intrauterine, peripartum, and postpartum. Most infants (~85%) acquire the infection perinatally or in the peripartum period. (3) Approximately 10% of neonates with HSV disease are infected postnatally, and 5% acquire the infection during the intrauterine period. (3)

Risk factors that increase the likelihood of HSV transmission from a pregnant woman who is shedding HSV genitally to her infant include:

1. Type of maternal infection (primary vs recurrent) (4)(5)(6)(7)(8)
2. Maternal antibody status (8)(9)(10)(11)
3. Longer duration of rupture of membranes (7)
4. Integrity of mucocutaneous barriers (using fetal scalp probe, incisions, etc) (8)(12)(13)
5. Mode of delivery (cesarean vs vaginal delivery) (8)

Infants born to women with primary (ie, first episode) genital HSV infection near the time of delivery are known to be at much greater risk of developing neonatal herpes than are infants who are born to women with recurrent genital HSV infection near the time of delivery (25%–60% vs <2%, respectively). (4)(5)(6)(7)(8) This increased risk is because of 2 main factors. First, there is a lower concentration of transplacentally passed HSV-specific antibodies in infants born to women with primary infections, because the pregnant woman has not had time to generate anti-HSV immunoglobulin G. (10) In addition, newly developed antibodies tend to be less effective in binding viral peptides. Second, a larger burden of the virus is shed vaginally and for a longer period in the genital tract of women with primary infection compared with those with recurrent HSV infection. (14) This was demonstrated in a landmark study of approximately 60,000 women in labor who did not have any symptoms of genital HSV infection at the time of delivery. In approximately 40,000 of these women, a vaginal swab was obtained for HSV detection within 48 hours of delivery (Fig 1). (8) Of these 40,000 women, 121 were identified to have asymptomatic shedding of HSV and had serum specimens available for HSV serologic testing, thereby allowing for the determination of first episode versus recurrent maternal infection. The trial found that 57% of infants born to women with primary infection who were shedding the virus in their genital tracts at delivery developed neonatal HSV; 25% of infants born to women with first episode nonprimary infection (had preexisting HSV-1 antibody and acquired HSV-2 or vice versa) developed neonatal HSV; and only 2% of infants born to women with recurrent HSV developed neonatal HSV (Fig 1). (8) This same large study also confirmed that cesarean delivery effectively decreased transmission of HSV to the neonate when women are shedding this virus in their genital tracts. (7) Despite this degree of protection, the risk of HSV transmission is not eliminated by cesarean delivery, and there are still cases of infants delivered via cesarean section who are found to have HSV. (15)(16)(17)

CLINICAL MANIFESTATIONS OF NEONATAL INFECTION AND DISEASE

Based on the extent of involvement, neonatal HSV infection is classified into 1 of 3 categories: disseminated disease; CNS infection; or skin, eyes, and mouth (SEM) infection. Disseminated disease involves multiple organs including, but not limited to, lung, liver, adrenal glands, brain, and skin. CNS disease involves the brain, with or without skin involvement, but no visceral organ dysfunction. SEM disease is limited only to these areas of the body. This classification system is predictive of morbidity and mortality, with disseminated disease having the most significant mortality and CNS disease having the most significant morbidity. (18)(19)(20)(21)(22)(23)(24)

Disseminated infection can manifest as severe hepatitis, disseminated intravascular coagulation, pneumonitis, and possibly CNS involvement (found in 60%–75% of cases).

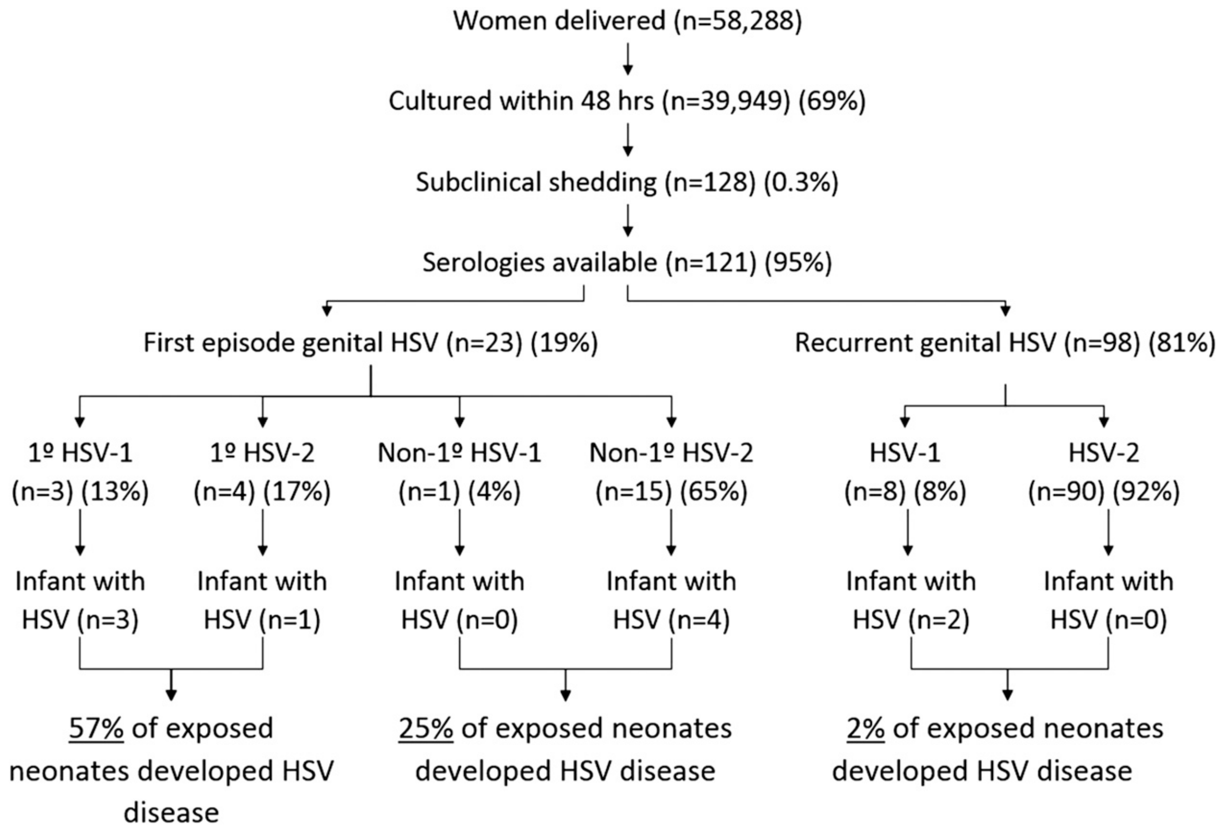
Women delivered (n=58,288)
Cultured within 48 hrs (n=39,949) (69%)
Subclinical shedding (n=128) (0.3%)
Serologies available (n=121) (95%)
First episode genital HSV (n=23) (19%)
Recurrent genital HSV (n=98) (81%)
1º HSV-1 (n=3) (13%)
1º HSV-2 (n=4) (17%)
Non-1º HSV-1 (n=1) (4%)
Non-1º HSV-2 (n=15) (65%)
HSV-1 (n=8) (8%)
HSV-2 (n=90) (92%)
Infant with HSV (n=3)
Infant with HSV (n=1)
Infant with HSV (n=0)
Infant with HSV (n=4)
Infant with HSV (n=2)
Infant with HSV (n=0)
57% of exposed neonates developed HSV disease
25% of exposed neonates developed HSV disease
2% of exposed neonates developed HSV disease

Figure 1. Risk of neonatal herpes simplex virus (HSV) disease as a function of type of maternal infection. Adapted from Brown et al. (8)

(19)(20)(21)(22)(23) The mean age at presentation of disseminated infection is approximately 11 days after birth. Interestingly, more than 40% of cases of disseminated HSV disease do not develop skin findings, which can complicate the ability to make the diagnosis promptly. (16)(19)(24)(25)

Neonatal HSV CNS disease can present as seizures (focal or generalized), lethargy, poor feeding, irritability, tremors, temperature instability, and bulging fontanelle. The mean age at presentation for CNS disease is approximately 16 days after birth. (19) Approximately 60% to 70% of infants with CNS disease will also have skin manifestations at some point in the disease course. (19)(24) Mortality is usually due to devastating brain destruction and atrophy, causing neurologic and autonomic dysfunction.

SEM disease is associated with the best outcomes, with virtually no mortality and with morbidity associated solely with cutaneous recurrences but no neurologic sequelae. In addition, infants with SEM disease are most likely to have skin lesions (in >80% of patients), which facilitates diagnosis and allows prompt initiation of antiviral treatment before the disease progresses to involve other organs. Presenting signs and symptoms of SEM disease include skin vesicles, fever, lethargy, and conjunctivitis. (19) The mean age at presentation for SEM disease is approximately 12 days after birth. (16)

DIAGNOSIS OF NEONATAL HSV DISEASE

The diagnosis of neonatal HSV infections requires sampling of multiple sites (1):

1. Swabs of mouth, nasopharynx, conjunctivae, and rectum should be tested for HSV surface cultures (if available) or polymerase chain reaction (PCR).
2. Specimens of skin vesicles should be tested for culture (if available) or PCR.
3. Cerebrospinal fluid (CSF) specimens should be tested for HSV PCR.
4. Whole blood samples should be tested for HSV PCR.
5. Alanine aminotransferase should be measured as an indicator of hepatic involvement (1)

In the past, the presence of red blood cells in CSF was suggestive of HSV CNS infection, likely as a result of relatively advanced disease due to diagnostic limitations; however, with the development of more advanced imaging and diagnostic capabilities, hemorrhagic HSV encephalitis is less commonly seen now, and as such, most HSV CNS

CSF indices do not have significant numbers of red blood cells. (1) Performance of whole blood PCR adds to the other diagnostic tools (surface and CSF cultures and CSF PCR), but should not be used as the sole test for ruling in or ruling out neonatal HSV infection. Furthermore, viremia and DNAemia can occur in any of the 3 types of neonatal HSV disease, so a positive whole blood PCR simply rules in neonatal HSV infection but does not assist in disease classification. HSV isolates from culture or HSV DNA detected on PCR can be typed to determine whether it is HSV type 1 or HSV type 2. Chest radiographs and liver function tests can aid in the diagnosis of disseminated infection. Histologic testing is of low yield because it has low sensitivity and should not be used for diagnosis. All infants with HSV disease, regardless of classification, need to have an ophthalmologic examination to look for ocular involvement such as uveitis, conjunctivitis, and keratitis. Infected neonates with any extent of disease manifestations should undergo neuroimaging studies (magnetic resonance imaging preferably, but head computed tomography or ultrasonography are acceptable) to establish baseline brain anatomy. (1) Later findings can include brain abscesses (particularly in the temporal lobe) or severe encephalomalacia. (1)

TREATMENT OF NEONATAL HSV DISEASE

Before antiviral therapies were developed and used, disseminated HSV disease caused death by 1 year of age in 85% of patients. In infants with CNS disease, mortality was 50% (Table 1). (22)(26) In a series of research studies conducted by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group between 1974 and

TABLE 1. **Mortality and Morbidity Outcomes Among Infants with Neonatal Herpes Simplex Virus Infection***

	TREATMENT			
EXTENT OF DISEASE	**PLACEBO (22)**	**VIDARABINE (20)**	**ACYCLOVIR (20) 30 MG/KG PER DAY**	**ACYCLOVIR (18) 60 MG/KG PER DAY**
Disseminated disease	n=13	n=28	n=18	n=34
Dead	11 (85%)	14 (50%)	11 (61%)	10 (29%)
Alive	2 (15%)	14 (50%)	7 (39%)	24 (71%)
Normal	1 (50%)	7 (50%)	3 (43%)	15 (63%)
Abnormal	1 (50%)	5 (36%)	2 (29%)	3 (13%)
Unknown	0 (0%)	2 (14%)	2 (29%)	6 (25%)
Central nervous system infection	n=6	n=36	n=35	n=23
Dead	3 (50%)	5 (14%)	5 (14%)	1 (4%)
Alive	3 (50%)	31 (86%)	30 (86%)	22 (96%)
Normal	1 (33%)	13 (42%)	8 (27%)	4 (18%)
Abnormal	2 (67%)	17 (55%)	20 (67%)	9 (41%)
Unknown	0 (0%)	1 (3%)	2 (7%)	9 (41%)
Skin, eye, and mouth infection	n=8	n=31	n=54	n=9
Dead	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Alive	8 (100%)	31 (100%)	54 (100%)	9 (100%)
Normal	5 (62%)	22 (71%)	45 (83%)	2 (22%)
Abnormal	3 (38%)	3 (10%)	1 (2%)	0 (0%)
Unknown	0 (0%)	6 (19%)	8 (15%)	7 (78%)

**Data are from an evaluation of 295 infants with neonatal herpes simplex virus infection conducted by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group between 1974 and 1997.*
Adapted from Kimberlin. (26)

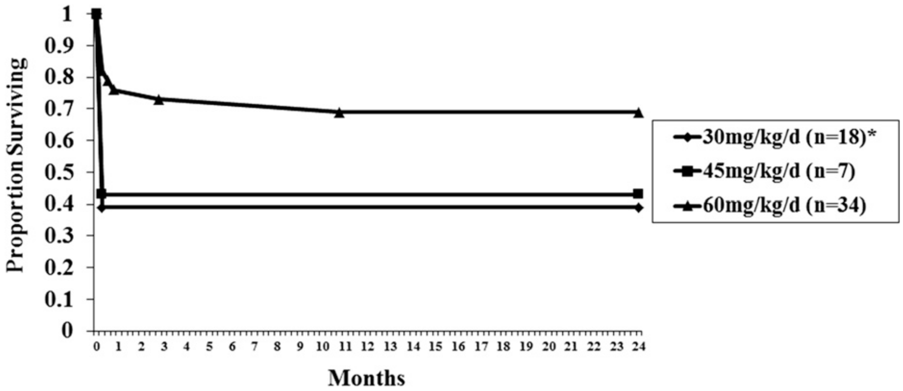

Figure 2. Mortality in patients with disseminated neonatal herpes simplex virus disease. Adapted from Kimberlin et al. (18)

1997, parenteral vidarabine, lower-dose acyclovir (30 mg/kg per day), and higher-dose acyclovir (60 mg/kg per day) were evaluated sequentially. (20)(22)(27) In the first of these studies, 10 days of vidarabine decreased mortality rates compared with placebo at 1 year both for patients with disseminated disease (rates decreased from 85% to 50%) and for those with CNS disease (rates decreased from 50% to 14%). Following comparison of lower-dose acyclovir with vidarabine for 10 days, parenteral acyclovir became the primary treatment choice for neonatal HSV disease because of its more favorable safety profile and its relative ease of administration (vidarabine required prolonged infusion times in large volumes of fluid). A subsequent study of higher-dose acyclovir for 21 days produced further reductions in 1-year mortality rates to 29% for disseminated disease (Fig 2) (18) and 4% for CNS disease (Fig 3). (18)

These series of studies determined that infants with neonatal HSV disease should be treated with parenteral acyclovir at a dose of 20 mg/kg per dose administered every 8 hours; the dosing interval may need to be increased in premature infants based on their creatinine clearance. (28) The treatment duration is 21 days for infants with disseminated disease or CNS disease, while infants with SEM disease should be treated for 14 days. (1) All patients with CNS involvement should have a repeat lumbar puncture near the end of the 21-day course of acyclovir to document that the CSF PCR is negative; if the PCR remains positive, another week of parenteral acyclovir should be administered, and lumbar punctures should be repeated in that manner until a negative CSF PCR is achieved. (19)(29)

The primary toxic effect of higher-dose parenteral acyclovir is neutropenia. (18) Thus, absolute neutrophil counts (ANCs) should be monitored twice weekly throughout the course of parenteral therapy. If ANC is less than 500/μL, either acyclovir treatment can be withheld or granulocyte colony-stimulating factor can be administered. Parenteral acyclovir dosing can resume when the ANC is higher than 750/μL. (18)

Oral acyclovir suppressive therapy for 6 months after acute parenteral treatment improves neurodevelopmental outcomes in infants with CNS disease. (1) It is well-known that HSV establishes latency in the sensory ganglia, and

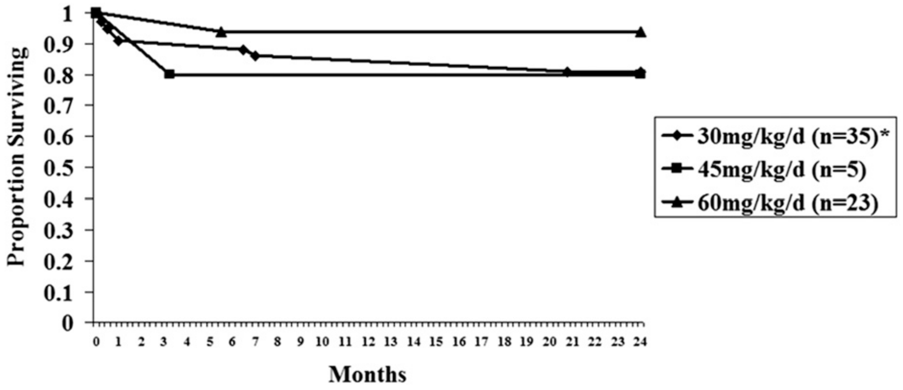

Figure 3. Proportion of surviving patients with neonatal herpes simplex virus disease affecting the central nervous system. Adapted from Kimberlin et al. (18)

TABLE 2. **Bayley Mental Scores at 12 months in Patients with CNS Involvement and SEM Disease***

	CASG 103 (CNS INVOLVEMENT STUDY)		CASG 104 (SEM STUDY)	
	ACYCLOVIR (N=16)	PLACEBO (N=12)	ACYCLOVIR (N=8)	PLACEBO (N=7)
Median	90.5	66.5	95	84
Adjusted mean	88.24[a]	68.12[a]	91.82[b]	84.92[b]
P value by ANCOVA	0.046		0.263	

**Patients were treated with placebo versus acyclovir suppression for 6 months. ANCOVA was adjusted for covariates at baseline which were unbalanced between treatment groups. ANCOVA=analysis of covariance; CASG=Collaborative Antiviral Study Group; CNS=central nervous system; SEM=skin, eyes, and mouth disease.*

[a] Head circumference at birth, birthweight, enrollment weight.

[b] Enrollment weight.

Adapted from Kimberlin et al. (30)

occasionally reactivates and causes recurrence of disease. However, it is not well-known if the virus subclinically reactivates in the brain after neonatal HSV has been treated, particularly with CNS involvement. If it does reactivate, it could be the cause of poor neurodevelopmental outcomes in patients with CNS involvement. A recent study involving infants with neonatal HSV with CNS involvement compared Bayley mental-developmental scores at 1 year in infants receiving suppressive therapy with acyclovir for 6 months versus infants receiving placebo (Table 2). (30) The study found that the acyclovir group had a significantly higher mean Bayley score than the placebo group (88.24 vs 68.12, *P*=.046). Suppressive acyclovir therapy also has been proven to prevent skin recurrences in HSV disease of all types. (30) Thus, infants should receive oral acyclovir at 300 mg/m² per dose 3 times daily as suppressive therapy for 6 months after the initial parenteral treatment course. This dose should be adjusted for growth monthly, and ANCs should be monitored at 2 and 4 weeks after starting therapy and then monthly thereafter while oral acyclovir is administered. (1)

OUTCOMES OF NEONATAL HSV WITH TREATMENT

Until recently, improvement in morbidity outcomes after antiviral treatment was less dramatic than mortality for neonates with disseminated disease or CNS disease. Oral acyclovir suppressive therapy has significantly improved the neurologic outcomes of infants with CNS involvement. (22) Without treatment, 50% of neonates who survived disseminated HSV disease were developing normally at 1 year of age. (22) With the use of higher-dose acyclovir for 21 days,

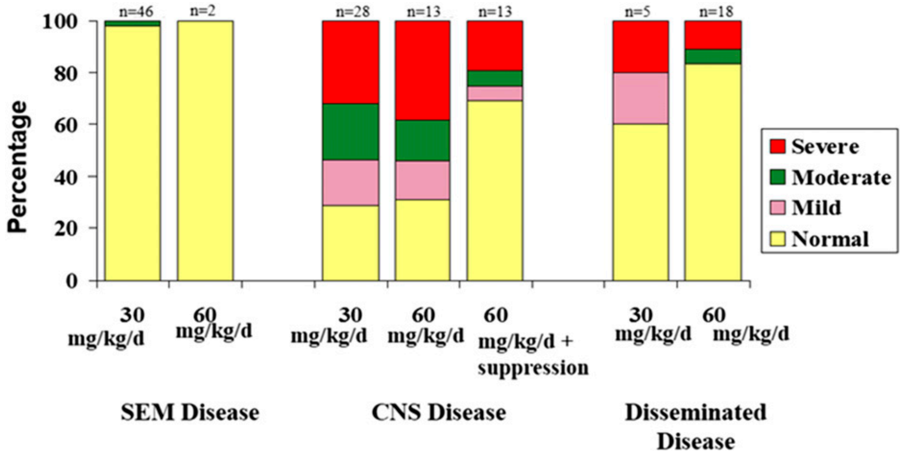

Figure 4. Morbidity among patients with known outcomes after 12 months of age. CNS=central nervous system; SEM=skin, eyes, and mouth disease. Adapted from Kimberlin et al. (18)(30)

the number of infants developing normally at 1 year of age after disseminated HSV disease has increased to 83% (Fig 4). (18) Similarly, for CNS HSV disease, 33% of patients demonstrate normal neurologic development at 1 year of age after 10 days of lower-dose acyclovir therapy, compared with 31% of children treated with higher-dose acyclovir for 21 days. However, with concomitant use of oral acyclovir therapy for 6 months, this percentage of infants with normal neurodevelopment at 1 year increases to 69% (Fig 4). (30) Morbidity of SEM disease also has dramatically improved since the introduction of antiviral treatment. In the preantiviral era, 38% of patients with SEM disease were developing normally at 1 year of age, but with antiviral therapy, this risk is eliminated completely (due to SEM disease not progressing to CNS or disseminated disease). (19)

CONCLUSION

Neonatal HSV disease is known to have devastating neurologic effects. Fortunately, over the past decades, much has been learned about the natural history, pathogenesis, diagnosis, and treatment of this severe infection. In the 21st century, neonatal HSV disease is treatable, and management recommendations have been standardized and implemented. As more knowledge is obtained, more questions are formed. These questions in turn drive the next series of studies, with further promise of continued advances for the future.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, prevention, and pathogenesis of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster.
- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster.

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* https://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Herpes-Simplex-Virus-Cold-Sores.aspx

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at http://patiented.aap.org.

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Human Immunodeficiency Virus Type 1 in the Premature Infant

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Education Gaps

With rapid changes occurring in the field of antiretroviral agents used to prevent and treat human immunodeficiency virus type 1 infection, neonatal clinical providers need to be aware of these advancements and recognize how these agents are used in the preterm infant population.

Abstract

Prematurity and low birthweight are seen frequently in infants with human immunodeficiency virus (HIV) type 1 infection, adding significant comorbidities and complicating the approach to treatment. HIV disease progression accelerates in the setting of an immature immune system. Recent cases have underscored the unique opportunity to not only limit progression, but also limit the establishment of HIV reservoirs that impede viral clearance by starting antiretroviral treatment (ART) early in the neonatal period. Although pediatric ART alternatives are increasing, there are still only few available agents for the treatment of neonates, especially premature and low-birthweight infants. Zidovudine is the only agent for which there is sufficient experience in premature infants, while being an intravenous alternative for infants in whom enteric administration is not possible. Nevirapine has been studied for prophylactic dosing in preterm infants. It is imperative that resources are devoted to the study of the safety and efficacy of ARTs for use during the neonatal period.

Objectives After completing this article, readers should be able to:

1. Discuss the use of human immunodeficiency virus (HIV) diagnostic tools in the neonate.
2. Describe the strategies to prevent mother-to-child transmission of HIV.
3. Describe the difference between prophylactic and treatment dosing of antiretroviral medications.
4. Identify the available antiretroviral agents for the neonatal age group.

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ABBREVIATIONS

cART	combination antiretroviral treatment
CYP	cytochrome
HIV	human immunodeficiency virus
MTCT	mother-to-child transmission
RT	reverse transcriptase
ZDV-TP	zidovudine triphosphate

INTRODUCTION

The rate of mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV) type 1 in the United States has dramatically declined in the past quarter century. HIV MTCT decreased from 22.6% among children whose mothers did not receive antiretroviral therapy (ART) to 7.6% between 1991 and 1994 in children who received neonatal single-agent zidovudine prophylaxis after their mothers received antenatal and intrapartum zidovudine. (1) In 2000, HIV MTCT further decreased to 1% to 2% among children who received neonatal single-agent zidovudine prophylaxis after their mothers received combination ART (cART) regimens. (2) Between 2002 and 2009, a US prospective cohort study found an MTCT of 0.65% when HIV-positive pregnant women received diverse cART regimens and infants were never breastfed. (3) In this study, half of the HIV-infected infants were born prematurely, compared with a prematurity rate of about 12.7% for the general US population. (4)

The preceding 2 decades have harbored many advances in the care of HIV-infected children. In particular, ART has evolved at a rapid pace. However, there is still a significant gap in the introduction of newer, more potent, less toxic, and better tolerated antiretroviral agents in young children, although some have been introduced gradually in recent years. (5)(6)(7) Within the pediatric age group, the gap is accentuated in newborns, most notably in premature infants, the most vulnerable group of HIV-infected individuals. Recent cases of infants treated very early in life who achieved a prolonged period of treatment-free suppression (8)(9) have generated considerable interest in the possibility of modifying the natural disease history by adopting early diagnosis and treatment modalities. (10)

The pathogenesis and virologic principles of HIV infection are similar during the neonatal period and older age groups. Low-birthweight and premature infants, however, constitute the most neglected population in terms of treatment experience, presenting both a challenge and an opportunity. A unique aspect of HIV infection in the neonatal period is the need to rely on virologic methods for establishing the disease diagnosis. In children born to HIV-positive mothers, one must take into account the perinatal route of acquisition, the possible previous exposure to antiretroviral agents during pregnancy, the higher plasma viremia levels observed in infants when compared with adult populations during acute infection, the high level of variability in pharmacokinetic parameters, immunologic immaturity, and the onset of infection in a growing individual.

Virtually all newborns born to an HIV-positive mother will have detectable antibodies against HIV type 1 (HIV-1), irrespective of the testing method used. (11) This situation precludes the use of rapid testing methods that have become widely available and underscores the need for reliable, rapid, and cost-effective nucleic acid diagnostic tools. At the present time, the commonly used virologic methods rely on measuring free plasma virus (HIV RNA) or cell-integrated virus (HIV DNA). Although extremely sensitive, both these methods introduce an element of delay in the diagnosis, usually measured in days, which complicates the early management of HIV-infected newborns.

The medical care of infants and children with HIV infection is continuously evolving, as results of new research are reported, new agents are approved, and new treatment modalities are adopted. Clinical trials guide appropriate dosing regimens in children and allow us to determine the safety and efficacy of these agents as they become available. Early diagnosis and prompt institution of cART can be effective in preventing disease progression. A significant reduction in disease progression and mortality was observed in a study in which cART was started at 6 weeks of age. (12) However, the same study showed that nearly 1 in 5 infants had a significant decline in the percentage of helper T cells ($CD4^+$) during the 3 to 4 preceding weeks. More ominously, 7 HIV-infected infants died and 16 developed signs of advanced HIV during the same pre-cART period. Furthermore, when treatment is delayed for 12 weeks, more than 60% of infants had developed advanced disease. Therefore, diagnosis needs to be attempted as soon as feasible.

Another important aspect is to recognize the increased risk of transmission experienced by women who acquire the infection during pregnancy. In particular, women infected during the third trimester have both a high risk of delivering prematurely and transmitting the virus to their offspring. A South African program identified seroconversion in 3.3% of pregnant women who tested negative earlier in pregnancy, accounting for 26% of HIV-infected infants, including a significant proportion of low-birthweight and preterm infants. (13)

Once diagnosis has been established, the immediate challenge is to identify a safe and effective antiretroviral regimen. Combination regimens using 3 antiretroviral drugs have been shown to enhance survival rates, reduce opportunistic infections, and delay disease progression. In the premature infant, this is of particular importance given the rapid pace of disease progression observed in untreated infants, complicated by the need to avoid short- and long-term toxicities, and development of drug resistance. Due to these complexities and the relative infrequency of this presentation, practitioners should be encouraged to seek consultation with a pediatric HIV specialist when faced with this situation. The Table provides a summary of antiretroviral treatments used for term and preterm infants.

TABLE. **Antiretroviral Agents for Term and Preterm Newborns in 2018**

CLASS	DRUG	USE IN TERM INFANTS	USE IN PRETERM INFANTS	OTHER
Nucleoside reverse transcriptase inhibitors	Zidovudine	Yes	Yes	Intravenous formulation is available
	Lamivudine	Yes		Dose for first month
	Emtricitabine	Yes		Dose for 0–3 months
	Stavudine	Yes		Frequent toxicities limit long-term use
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	Yes	Only ≥34 weeks' gestational age	
Protease inhibitors	Lopinavir/ritonavir	Only after 2 weeks of age and 42 weeks' postmenstrual age	No	
Integrase inhibitors	Raltegravir	Yes	No	Competes with bilirubin for protein binding and elimination

ZIDOVUDINE

Zidovudine is a synthetic nucleoside analogue used in the treatment of infections caused by HIV-1. Intracellularly, zidovudine is phosphorylated to its active 5′-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture. The finding that an antenatal, intrapartum, and 6-week newborn regimen of zidovudine reduced perinatal transmission of pediatric HIV infection by nearly 70% was a landmark in HIV MTCT prevention. (1) The pharmacokinetics of zidovudine were evaluated in infants from birth to 3 months of age. Zidovudine elimination was determined immediately after birth in 8 neonates exposed to zidovudine in utero; the half-life was found to be 13.0 ± 5.8 hours. In neonates 14 days of age or younger, bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric patients older than 14 days. (14)

Zidovudine pharmacokinetics were also studied in preterm infants. (15) A total of 38 HIV-exposed infants born before 35 weeks of gestation who were receiving zidovudine as part of standard prophylaxis to reduce perinatal HIV transmission were enrolled into a pharmacokinetic study during the first 5 days after birth. Infants were given intravenous zidovudine 1.5 mg/kg every 12 hours until 2 weeks of age, then 2.0 mg/kg every 8 hours until 6 weeks of age. Zidovudine was generally well tolerated in this high-risk population. The authors recommended 1.5 mg/kg (intravenous) or 2.0 mg/kg (oral) every 12 hours with an increase in frequency to every 8 hours at 2 weeks of age (for infants with birth gestational age ≥30 weeks) or at 4 weeks (for infants with birth gestational age <30 weeks). To date, zidovudine is the only drug that has been sufficiently studied in premature infants.

LAMIVUDINE

Lamivudine is a cytosine nucleoside analogue RT inhibitor used in the treatment of infections caused by HIV-1 and hepatitis B virus. It undergoes anabolic phosphorylation by intracellular kinases to form lamivudine 5′-triphosphate. The active anabolite prevents HIV-1 and hepatitis B viral replication by competitively inhibiting viral RT and terminating proviral DNA chain extension. Lamivudine is widely distributed into total body fluids. Lamivudine concentrations in maternal serum, amniotic fluid, umbilical cord, and neonatal serum are comparable, indicating that the drug diffuses freely across the placenta. In postpartum women, lamivudine is secreted into breast milk. Lamivudine and zidovudine exhibit synergy in vitro, (16)(17) which provides the rationale for combining these 2 agents in the treatment of HIV-1 infection. More importantly, lamivudine induces a lamivudine-resistant methionine-to-valine substitution mutation at codon 184 (M184V mutation) at the YMDD motif or region in HIV-1 RT. This mutation is associated with a delay in the emergence of zidovudine-resistant mutants in zidovudine-naïve patients, restoration of zidovudine sensitivity in some patients already possessing zidovudine-associated resistance mutations, impairment of HIV-1 replication capacity and virulence ("fitness"), and a reduced ability of the HIV-1 *env* gene to mutate. (18)(19)(20)

Lamivudine alone and in combination with zidovudine has been studied in 20 neonates, in whom therapy began 12 hours after birth and was continued for 1 week. (21) The pharmacokinetic parameters of lamivudine were not altered by the coadministration of zidovudine. It was observed that lamivudine's peak serum concentration occurred later, the areas under the plasma drug concentration-time curve and peak concentration were higher, and neonatal lamivudine clearance was about half that in pediatric patients. In view of the lower drug clearance-to-fraction absorbed in neonates at 1 week of age, the dosage of lamivudine in these patients should be reduced from 4 mg/kg twice daily (the recommended dosage for infants and children) to 2 mg/kg twice daily. However, there is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age ranges greater than 3 months. (22)

NEVIRAPINE

Nevirapine is a non-nucleoside RT inhibitor with activity against HIV-1. This drug remains a mainstay of therapy, especially in resource-limited settings. (23) Nevirapine is structurally a member of the dipyridodiazepinone chemical class of compounds. It is readily absorbed after oral administration, and is highly lipophilic and nonionized at physiologic pH. In vivo trials in humans and in vitro studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome (CYP) P450 (oxidative) metabolism to several hydroxylated metabolites. (24) Oxidative metabolism of nevirapine is mediated primarily by CYP P450 isozymes from the CYP3A and CYP2B6 families, though other isozymes may have a secondary role. Nevirapine is an inducer of hepatic CYP P450 metabolic enzymes 3A and 2B6 by about 20% to 25%, as indicated by erythromycin breath test results and urine metabolites. In adults, autoinduction of CYP3A- and CYP2B6-mediated metabolism leads to an approximately 1.5- to 2-fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to 2 to 4 weeks of dosing with 200 to 400 mg per day. (25) Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma, from approximately 45 hours (single dose) to approximately 25 to 30 hours following multiple dosing with 200 to 400 mg per day. This resulted in the need for a lead-in dose of 200 mg daily for 2 weeks, followed by 200 mg twice daily. Older pediatric subjects receiving nevirapine at 150 mg/m^2 twice daily (after a 2-week lead-in of 150 mg/m^2 daily) produced geometric mean or mean trough nevirapine concentrations between 4 and 6 μg/mL, similar to adult data. (26) Evaluation of pediatric subjects 1 to 3 months of age showed that plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the pediatric population, but were more variable among subjects, particularly in the younger population. (27)

The increased rate of resistance observed with the widespread use of nevirapine for MTCT prophylaxis (28)(29) led to many practitioners opting for treatment dosing of HIV-exposed newborns. This modality was undertaken in an effort to prevent the emergence of resistance. Moreover, results of a randomized study showed that nevirapine was inferior to lopinavir-ritonavir in young infants, but not in older children, questioning the use of the lead-in dose in this population. (30) For the premature infant, only preliminary data are available. In premature infants, most data have been accumulated in prophylaxis studies, where the target trough concentration is above 0.1 μg/mL compared with the more than 3.0 μg/mL dose needed for treatment regimens. These studies showed a decrease in drug clearance inversely proportional to gestational age. (31)(32) To date, treatment doses of nevirapine for premature infants remain investigational, because data are only available for infants of 34 weeks' or longer gestation who weigh 1.5 kg or more. For these patients, the recommended dose is 4 mg/kg per dose twice daily for the first week, increasing to 6 mg/kg per dose twice daily thereafter. (33)

OTHER ANTIRETROVIRAL AGENTS

Stavudine is a nucleoside RT inhibitor that was widely used in the pediatric population. Stavudine is virologically antagonistic with zidovudine, and the 2 agents should not be used together. Stavudine was studied in full-term neonates, in whom a dose of 0.5 mg/kg twice daily for the first 2 weeks of age was recommended with an increase to 1 mg/kg twice daily subsequently. However, because of the observed increased risk of adverse effects and overlapping toxicities, such as mitochondrial toxicity, insulin resistance, dyslipidemia, lipoatrophy, especially after long-term use, it is no longer recommended.

Emtricitabine and lamivudine have long been considered interchangeable. Both agents share similar resistance profiles and lack additive benefit, precluding their use together. Emtricitabine, similar to lamivudine, has relatively low toxicities, and evidence suggests that emtricitabine and lamivudine have equivalent efficacy and toxicity in antiretroviral-naive patients. Although the neonatal dose of emtricitabine has been established as 3 mg/kg daily and its dosing frequency is attractive, lamivudine has been generally preferred because of the larger experience accumulated with this drug.

Lopinavir-ritonavir has been for many years one of the most effective antiretrovirals used in children. However, the adverse experience with lopinavir-ritonavir in neonates highlights the risks of using these drugs in neonates without appropriate safety and pharmacokinetic data. Life-threatening cardiovascular, renal, and central nervous system toxicities were reported to the Food and Drug Administration in 10 infants receiving lopinavir-ritonavir oral solution during the first weeks of age. (34) Eight of these infants were born prematurely. These toxic effects included bradycardia, complete atrioventricular block, heart failure, renal failure, respiratory failure, metabolic acidosis, hypotonia, central nervous system depression, and cardiogenic shock. The lopinavir-ritonavir oral solution contains ethanol (42.4% wt/vol) and propylene glycol (15.3% wt/vol), and the contributions of lopinavir, ritonavir, ethanol, and propylene glycol exposure to the observed toxicities are not clear. This resulted in a recommendation to avoid use of this drug until infants are at least 42 weeks' postmenstrual age.

Integrase inhibitors have generated much interest as an alternative therapy for neonates, given the successful gradual introduction of these potent agents in older pediatric age groups. Data are lacking to formulate a safe dosing recommendation in neonates, and studies are ongoing. Raltegravir is commonly used in antenatal ART regimens. This drug readily crosses the placenta, and neonatal elimination after maternal administration has been studied. Raltegravir washout was found to be highly variable, with the half-life ranging from 9.3 hours to more than 7 days. (35) Moreover, raltegravir is eliminated by uridine 5′-diphospho-glucuronosyltransferase 1, polypeptide A1 (UGT1A1), the same enzyme that metabolizes bilirubin and whose activity is very low in the first few days after birth, therefore competing with bilirubin for protein binding and for elimination through glucuronidation. (36) High plasma concentrations of raltegravir may lead to increased plasma concentrations of free unconjugated bilirubin, increasing the risk for indirect hyperbilirubinemia and kernicterus, particularly in preterm infants who have lower bilirubin elimination and albumin-binding capacity, and an immature blood-brain barrier. Raltegravir use in neonates is of interest because it has potential benefit as both prophylaxis and treatment. Based on the results of IMPAACT P1110, which evaluated the pharmacokinetics of raltegravir in 42 full-term, HIV-exposed newborns, the oral granule raltegravir formulation was recently approved for neonates ≥37 weeks of gestation and weighing ≥2 kg; the dose is 1.5 mg/kg once daily from birth to age 7 days, and 3 mg/kg twice daily from 8 to 28 days of age. The first dose of raltegravir needs to be delayed until 24-48 hours after birth if the mother received raltegravir as part of her antiretroviral regimen. To date, no data are available for preterm newborns or term infants weighing less than 2.0 kg. (37)

CONCLUSIONS

Since the introduction of zidovudine, monotherapy has been invariably followed by the emergence of resistant strains. The high-level viral replication of HIV, in conjunction with the known mutation rate of its RT, results in the emergence of resistance that can be detected as early as 24 hours after monotherapy is started. Modeling of single-drug regimens led to the observation of the emergence of resistance within 24 hours, while dual-drug agents take about 90 days for this to occur. Effective treatment forces the virus to mutate simultaneously at multiple positions in its genome, which is achieved with the use of 3 agents.

The overall goal of ART is to preserve immune function, limit the size of viral reservoirs, and reduce the emergence of antiretroviral resistance. In this setting, the use of zidovudine monotherapy could be seen as counterproductive, and therefore practitioners need to seek dual or, ideally, 3-drug regimens. At the present time, these regimens could only be safely constructed in consultation with a pediatric HIV specialist, because many considerations need to be taken into account, especially comorbidities associated with prematurity. Every patient needs to be carefully and individually evaluated, and a general regimen cannot be safely recommended. In some clinical situations, a 2-drug regimen could be appropriate temporarily until the third agent could be given safely. One important additional factor that needs to be taken into account when treating a premature infant with HIV is the family's socioeconomic situation and support system. In the author's experience, a multidisciplinary approach is essential, because of the presence of multiple comorbidities, and the use of multiple agents given several times a day to a small infant as an outpatient is difficult enough under ideal circumstances. Therefore, high levels of support are essential for a successful outcome when treating this vulnerable population.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, prevention, and pathogenesis of perinatal HIV infection.
- Know the clinical manifestations and diagnostic features of perinatal HIV infection.
- Know the treatment and complications of perinatal HIV infection.

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Jaime G. Deville

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Index of Suspicion in the Nursery

1 A Rare Case of Antenatal Hemorrhagic Stroke and Recurrent Purpura Fulminans in a Preterm Newborn

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CASE REPORT

A female infant is born prematurely at 33 weeks of gestation to consanguineous parents (parents are first cousins). The mother has had 2 uneventful pregnancies and both children are well. There is no history of recurrent miscarriages, stillbirth or neonatal stroke, or family history of bleeding diathesis or clotting disorders. Antenatal scans had revealed the fetus to be growing well until 30 weeks of gestation, when the weight dropped from the 40th to the 3rd percentile. At that time, the amniotic fluid volume, Doppler scan, and placental blood flow were normal. The mother had been asymptomatic, with normal blood cell count and erythrocyte sedimentation rate.

Now at 33 weeks of gestation, the mother presents to the emergency department with reduced fetal movements over the previous week. She is admitted for observation. Antenatal ultrasonography confirms the earlier findings of intrauterine growth restriction and documented normal amniotic fluid volume and Doppler scan. She remains clinically well. However, cardiotocographic monitoring the next day reveals the presence of repeated decelerations suggestive of nonreassuring fetal status, prompting an urgent cesarean delivery.

The infant is well at birth, and has a good cry. Apgar scores are 6 and 9 at 1 and 5 minutes, respectively. Birthweight is 1,160 g (<3rd percentile), length 39 cm (3rd-10th percentile) and head circumference 27.5 cm (3rd percentile). Soon after birth, the infant develops respiratory distress secondary to partially compensated metabolic acidosis (pH, 7.32; partial pressure of carbon dioxide, 19.5 mm Hg [2.6 kPa]; partial pressure of oxygen, 111 mm Hg [15 kPa]; base excess, −12; and bicarbonate, 14 mEq/L [14 mmol/L]). Clinical examination findings are unremarkable and vital signs are normal. No hypoglycemia or electrolyte abnormality is noted. Laboratory investigations on day 1 reveal thrombocytopenia (platelet count $39\times10^3/\mu L$ [$39\times10^9/L$]) and coagulopathy (prothrombin time 60 seconds, activated partial thromboplastin time >180 seconds) in the absence of clinical bruising and external hemorrhage. The hematologic abnormalities are promptly corrected with platelet and fresh frozen plasma (FFP) transfusions. She is empirically treated with intravenous antibiotics because of unexplained thrombocytopenia.

Cranial ultrasonography on day 1 after birth shows bilateral intraventricular hemorrhage with echogenicity in the temporoparietal area. Serial cranial ultrasonography in the ensuing weeks shows progression of hemorrhage, resulting in dilation of both lateral and third ventricles (Fig 1). She appears pale and had tachycardia throughout the first 2 weeks after birth, associated with persistent

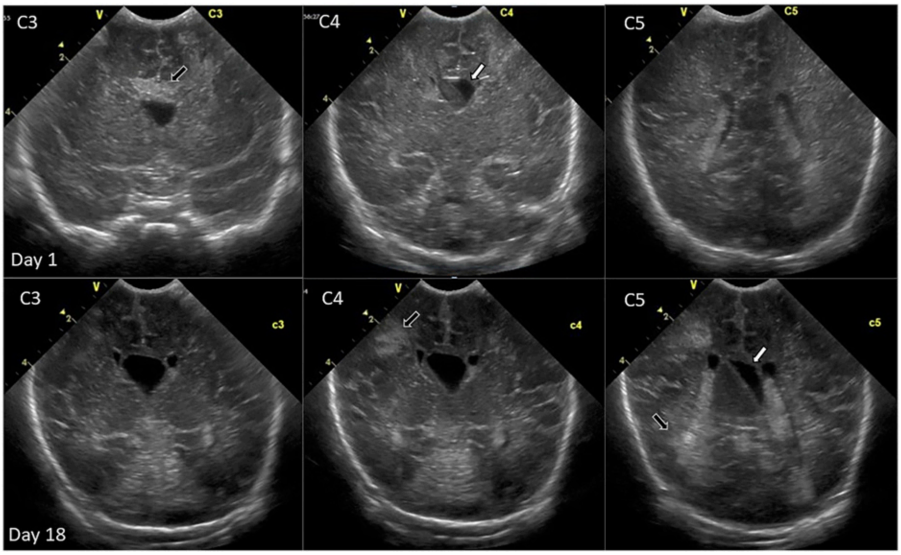

Figure 1. Top row: Coronal section of cranial ultrasonographic images obtained on day 1 after birth. Note the focal hyperechoic area in the anterior aspect of the corpus callosum (black arrow), suggestive of a periventricular bleed. A fluid-fluid level in the cavum vergae (white arrow) indicates intraventricular hemorrhage. Bottom row: Coronal section of cranial ultrasonographic images obtained on day 18 after birth. Note the ventricular dilation (white arrow) and multiple areas of echogenicity in the frontal and parieto-occipital regions (black arrow), suggestive of progression of hemorrhage when compared to previous images.

decline of hemoglobin from 16.6 g/dL (160 g/L) to 9.2 g/dL (92 g/L) despite receiving red blood cell transfusions.

Brain magnetic resonance imaging (MRI) on day 18 after birth shows multiple hemorrhagic lesions (Fig 2). The widespread distribution of affected areas clearly does not correspond to arterial ischemia and suggests the possibility of venous thromboembolism. Amplitude-integrated electroencephalography demonstrates episodes of electrographic seizures that are difficult to control despite multiple phenobarbital boluses. Seizures are finally controlled with phenobarbital 6 mg/kg per day and levetiracetam 80 mg/kg per day.

In consultation with pediatric hematology, thrombophilia screening is undertaken to investigate the etiology of the stroke. The diagnosis of severe protein C deficiency is rendered after an extremely low protein C level of 1% (age-specific reference range 12%–44%) is found. Protein C level is low in both parents (63% and 49%; adult reference range 70%–140%). Initial management consists of daily FFP transfusions (40 mL/kg per day), which transiently raises the protein C level to 10% but this is poorly sustained. A second MRI/magnetic resonance angiography of the brain on day 44 after birth shows interim development of sagittal sinus thrombosis as well as evolving encephalomalacia (Fig 3). Subcutaneous enoxaparin treatment is commenced on day 50 after birth in view of sagittal sinus thrombosis in the absence of further bleeding. Despite achieving therapeutic anti-Xa levels of 0.5 to 1.0 U/mL, she develops purpura fulminans 10 weeks after birth (Fig 4), which then recurs 20 weeks after birth during an episode of rotavirus gastroenteritis (Fig 5).

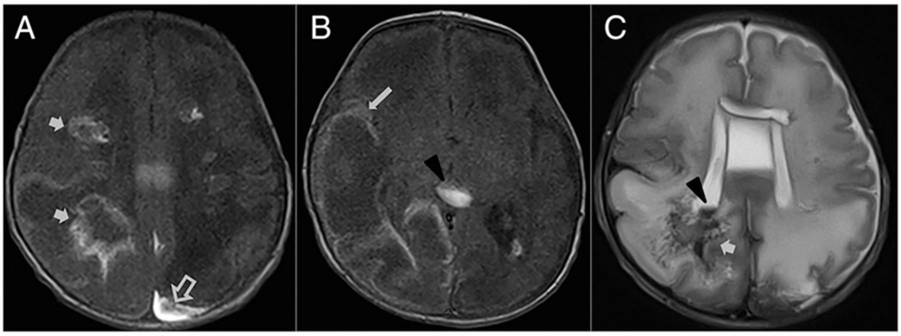

Figure 2. Noncontrast magnetic resonance imaging of the brain on day 18 after birth showing axial T1 (A, B) and T2 (C) sections. Multiple areas of ischemia and hemorrhage can be seen, involving brain parenchyma (thick short arrows), subdural spaces (open arrow), subarachnoid spaces (thin arrow), and intraventricular spaces (arrowheads).

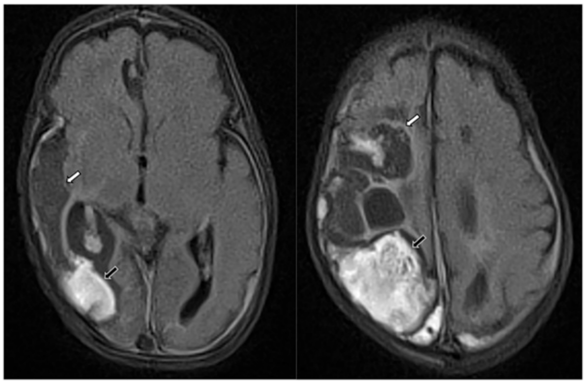

Figure 3. Magnetic resonance imaging of the brain (T1-weighted axial sections) on day 44 after birth showing extensive areas of cystic encephalomalacia (white arrows) and residual products of parenchymal hemorrhages (black arrows), predominantly affecting the right parieto-occipital lobe.

From the third month after birth, there is no further intracranial hemorrhage. Neurologically, the infant has marked head lag and poor truncal tone, with evolving signs of an upper motor neuron impairment involving all 4 limbs. She requires nasogastric tube feeding because of sucking-swallowing-breathing incoordination. Frequent accumulation of oral secretions places her at risk for aspiration.

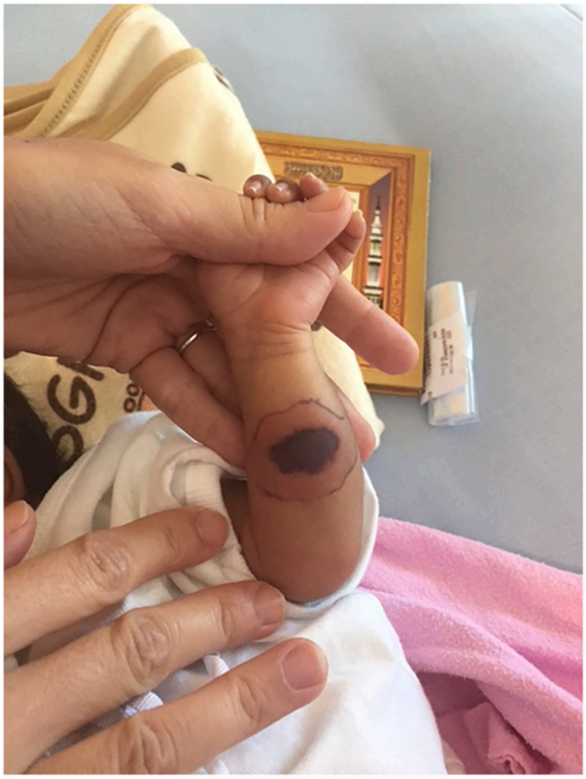

Figure 4. Necrotic skin lesions *(purpura fulminans)* over the ventral aspect of the left forearm.

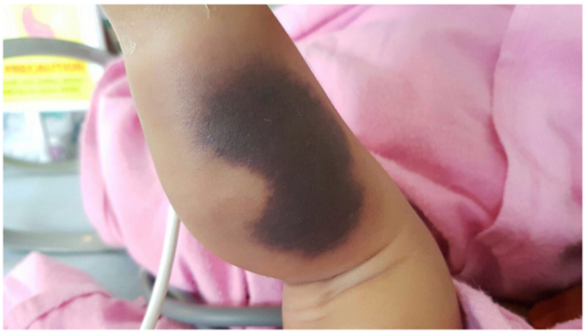

Figure 5. Recurrence of purpura fulminans with necrotic skin lesions over the patient's lower limbs during an episode of rotavirus gastroenteritis.

Her parents receive counseling about the underlying etiology of intracranial hemorrhage and definitive management plans, including the need for long-term replacement therapy with protein C concentrate. Taking into consideration the cost of regular protein C concentrate and the severity of encephalomalacia with high likelihood of poor neurodevelopmental outcomes, a joint decision is made to pursue limited medical care. This consisted of intermittent FFP transfusions, subcutaneous enoxaparin, and physiotherapy.

DISCUSSION

Severe congenital protein C deficiency is frequently diagnosed late or underdiagnosed because of its rarity and variable presentation. A frequent mode of presentation is neonatal purpura fulminans or disseminated intravascular coagulation. (1) It may also be associated with massive thrombosis or in utero death. Case ascertainment often depends on whether mothers with unexplained miscarriage or stillbirth undergo thrombophilia screening. Investigations in cases of neonatal stroke are often not offered because parents are asymptomatic as in the case reported here. Thus, the prevalence of congenital protein C deficiency of 1 in 4 million may be grossly underestimated.

Interpretation of protein C levels in a newborn is fraught with difficulty. Physiologically, newborn infants have low levels of protein C—a term neonate has protein C levels equivalent to 35% of normal adult levels, whereas a preterm neonate has 10% to 15% of normal adult levels, but this has not been universally studied in a preterm neonatal population. (2) Levels are further reduced in the setting of acute thrombosis and hence, thrombophilia screening is usually not advised during such an episode. However, there may be value in testing to exclude severe deficiencies.

In our patient, the declining fetal growth at the 30-week antenatal scan and the paucity of fetal movement from the

32nd week of gestation were red flag features of fetal compromise. Given the severity of the protein C deficiency, it was surprising that she did not initially present with purpura fulminans. We conjecture that the predilection of cerebral vessels for hemorrhage was due to disturbances in cerebral blood flow coupled with intrinsic fragility of the germinal matrix of an immature brain. Also, the presentation of purpura fulminans 10 weeks after birth illustrates that it can occur at any point of the disease process.

With the initial presentation of unexplained metabolic acidosis and thrombocytopenia, clinicians are inclined to investigate for neonatal sepsis first. In retrospect, the paucity of signs to support a diagnosis of sepsis and the presence of severe intraventricular hemorrhagic infarct, out of proportion to the degree of prematurity, would suggest a need to consider alternative etiologies for the thrombocytopenia and acidosis.

There are published recommendations based on expert opinions for initial and long-term treatment of patients with severe protein C deficiency. (3) The standard initial treatment is 10 to 20 mL/kg of FFP every 12 hours until clinical symptoms resolve. Human plasma–derived viral-inactivated protein C concentrate given intravenously has now become available and is the treatment of choice for patients with severe deficiency. (4) In severe protein C deficiency, it is notable that the reported complications are not only thrombotic but also hemorrhagic, reflecting the delicate balance between pro- and antithrombotic forces and the need to approach this with great care. In our patient who developed initial intracranial hemorrhage and later MRI evidence of sagittal sinus thrombosis, the decision to institute procoagulation therapy initially but anticoagulation later was made in consultation with a pediatric hematologist.

The twice-daily FFP transfusions (40 mL/kg per day) produced only a transient rise in protein C levels for our patient. We speculate that the later lack of efficacy might have been related to the highly variable protein C content of each FFP transfusion. Although protein C concentrate is the most reliable source of protein C delivery, this was not started because of the parents' decision to provide limited medical care after having considered the cost and poor neurologic prognosis.

The most widely used long-term treatment is oral anticoagulation to maintain an international normalized ratio in the range of 2.5 to 3.5. Other options such as low-molecular-weight heparin and protein C concentrate administration have been tried with excellent results. Warfarin is the preferred anticoagulant because of its lower cost and ease of administration over the long-term. (5) However, it requires close monitoring and dose adjustment in the initial period, issues that may be problematic for a premature infant with limited blood volume. In consultation with the pediatric hematologist, the patient was given subcutaneous enoxaparin from 2 months after birth when the intracranial hemorrhage had stabilized, achieving an anti-factor Xa level of 0.5 to 1 U/mL. Enoxaparin was favored over warfarin because

1) protein C levels cannot be reliably measured in patients receiving warfarin,
2) enoxaparin minimizes the need for routine blood tests,
3) there is a risk of warfarin-induced skin necrosis, (6)
4) there are reports of drug-drug interactions between antiepileptic drugs and warfarin, and
5) there are concerns of future interaction with food.

Monitoring D-dimer levels was said to be useful to confirm the adequacy of anticoagulation. (4)(7)

Although the predominant pattern of inheritance is autosomal dominant, autosomal recessive forms have been reported. The patient in this report was likely to be of the latter type because of parental consanguinity and the assumption that they had 12.5% genes in common. Genetic testing is vital for risk counseling in future pregnancies. Although the parents declined this on the basis of having completed their family, there remains a role for screening siblings of the proband to provide opportunity for genetic counseling.

In conclusion, we recommend that newborns with hemorrhagic cerebral infarcts or thrombosis be screened for hereditary thrombophilias including protein C deficiency, especially in cases of parental consanguinity or when the severity of hemorrhage is out of proportion to the degree of prematurity. It is difficult to achieve adequate protein C levels without protein C concentrates, which is expensive and not easily available in many countries. The challenges in decision making regarding anticoagulation in the presence of hemorrhage and the complexity of care required are best managed by a multidisciplinary team for optimal outcomes.

Acknowledgments

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American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and pathophysiology of congenital and acquired thrombotic disorders.
- Know the clinical and laboratory features, management, and potential adverse effects of treatment of congenital and acquired thrombotic disorders.

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2 Refractory Respiratory Failure and Pneumothorax in a Full-Term Newborn

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AUTHOR DISCLOSURE Drs Reed, Arya, Dufendach, and Leino have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant with a birthweight of 2,925 g is delivered at 38 6/7 weeks of gestation by a 32-year-old gravida 1, para 1 mother. The pregnancy is uncomplicated, and the mother's evaluation for infection before delivery is negative. The birth occurs via precipitous vaginal delivery and is uneventful except for terminal meconium. At delivery, the infant is initially vigorous with an appropriate heart rate and tone, but she subsequently requires resuscitation because of increased work of breathing and oxygen saturation in the low 60s. She is treated with positive pressure ventilation, and the fraction of inspired oxygen is increased to 100%. Despite positive pressure ventilation, her physical examination findings and oxygen saturation do not improve. Her 1- and 5-minute Apgar scores are 7 each. Initial chest radiography shows a right-sided pneumothorax and pneumomediastinum. Her first capillary blood gas is notable for a pH of 6.9, a partial pressure of carbon dioxide (P_{CO_2}) of 101 mm Hg (13.4 kPa), and a base deficit of 13. Needle decompression of the right chest is attempted, after which the infant is intubated and mechanical ventilation is started. Screening infectious laboratory tests are performed and empirical broad-spectrum antibiotics are started. The infant is then transferred to a tertiary care facility for further care. Upon arrival, the infant is switched to a high-frequency oscillator. At this point, repeat chest radiography shows bilateral pneumothoraces and pneumomediastinum, so bilateral chest tubes are placed.

DISCUSSION

Despite oscillatory ventilation, 100% fraction of inspired oxygen, and surfactant, the infant's oxygen saturation remained in the 80s. An echocardiogram was unremarkable. The capillary gas at 2.5 hours after birth improved slightly, with a pH of 7.03, P_{CO_2} of 90 mm Hg (12 kPa), and base deficit of 7. Inhaled nitric oxide and inhaled epoprostenol were empirically initiated. Because of persistent hypotension and hemodynamic instability, the infant started treatment with epinephrine and vasopressin, as well as milrinone and hydrocortisone. She had brief clinical improvement, and 8 hours after birth, her capillary gas pH was 7.20, with a P_{CO_2} of 55 mm Hg (7.3 kPa) and base deficit of 6. However, she progressively deteriorated over the next 24 hours with prolonged oxygen desaturation and hypotension, leading to the initiation of extracorporeal membrane oxygenation (ECMO).

Differential Diagnosis

The infant's initial presentation was concerning for meconium aspiration syndrome with persistent pulmonary hypertension. However, the continued clinical deterioration despite increasing support made this diagnosis less probable. Sepsis was also considered, and the infant was treated with empirical antibiotics, but the lack of improvement despite intervention made this diagnosis less likely as well. Echocardiography ruled out cardiac etiologies such as total anomalous pulmonary vein return, leaving primary pulmonary pathology as the most likely cause for the patient's disease. Persistent respiratory failure requiring continuation of ECMO led to consideration of the diffuse developmental disorders of the lung, including acinar dysplasia (AD), congenital alveolar dysplasia (CAD), and alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV). The differential also included congenital surfactant deficiencies (surfactant protein B deficiency, surfactant protein C deficiency, *ABCA3* deficiency).

The Condition

Normal lung development occurs in 5 phases: the embryonic (3–7 weeks after conception), pseudoglandular (5–17 weeks after conception), canalicular (16–25 weeks after conception), saccular (24–36 weeks after conception), and alveolar (36 weeks after conception through adolescence) phases. (1) Lung development can be arrested during any phase, and the timing of the arrest determines the severity of disease. (1) Developmental lung dysplasia was noted as early as 1948 by MacMahon, (2) but because of the rarity of the developmental lung dysplasias, research on the topic is limited, leading to an incomplete understanding of the disease. Incidence and prevalence of the neonatal developmental lung diseases remain unknown, (3) and it remains unclear whether AD, CAD, and ACD/MPV are individual diseases or part of a spectrum of the same disease. (3)

Lung growth arrest during the pseudoglandular or early canalicular phase leads to the diffuse impaired pulmonary acinar development seen in AD. The saccular or alveolar spaces necessary for gas exchange are completely absent, and the lungs may be smaller than expected for the patient's gestational age. Radiologic findings may include hyperinflation, interstitial prominence, and diffuse increased pulmonary density. These patients are typically born at term gestation, and death occurs within hours of delivery. (4) In patients with CAD, lung development is arrested in the late canalicular or early saccular phases. These patients have incomplete alveolarization and absence of secondary septation, though the lungs are normal in size. Patients with CAD are typically born at term gestation, and death typically occurs in the neonatal period but later than in AD. (5) Disorganized pulmonary maldevelopment during the saccular and alveolar phases leads to ACD/MPV. This condition is associated with defects in the *FOXF1* gene. (6) More than 90% of patients are born at term, and acute hypoxemic respiratory failure develops within 48 hours. (6) Chest radiograph is usually normal but there may be a diffuse ground glass pattern. Although ACD/MPV is also fatal in the neonatal period, 4 known cases presenting as late as 7 months of age are noted in the literature. However, all symptomatic patients have died. (6)

Treatment

Initial therapy for patients with this presentation is supportive. Patients require intubation and potentially ECMO. However, as noted here, these diseases are fatal and to date, there have been no effective life-saving therapies. High-resolution computed tomography may be useful for demonstrating the type of abnormality, extension, and distribution of disease. (4) If a patient is stable with supportive care, a biopsy and genetic testing for the *FOXF1*, *NKX2.1*, *SFTPB*, *SFTPC*, and *ABCA3* genes may be beneficial if lung transplantation is a consideration. (4) In one case, prenatal testing helped avoid escalation to ECMO in a symptomatic patient. (7)

Progression

The infant was given maintenance ECMO for 19 days, during which she developed seizures, and left-sided

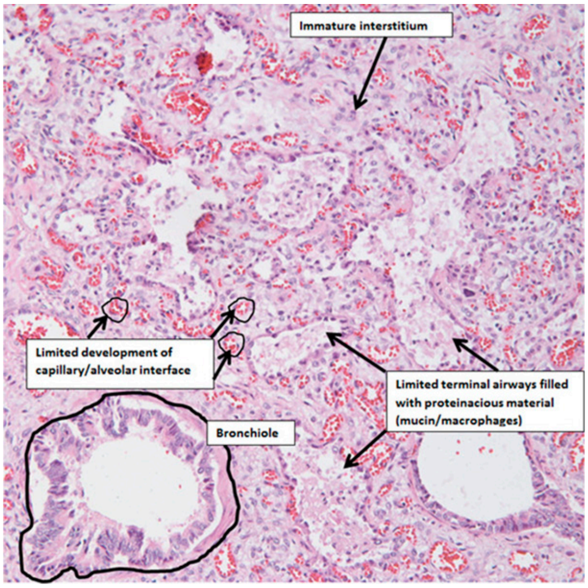
Immature interstitium
Limited development of capillary/alveolar interface
Limited terminal airways filled with proteinacious material (mucin/macrophages)
Bronchiole

Figure. Hematoxylin-eosin staining of lung tissue obtained in an autopsy of a term infant. Appearance of lungs with histologic maturity is shown at ∼23 weeks of gestation. Alveolar development is limited, with persistent interstitium and significant mucus plugging.

parenchymal bleeding was noted. Following ECMO decannulation, the infant had persistent respiratory decompensation for 36 hours, and she died shortly after withdrawal of support with elective extubation on day 24 after birth.

The infant's autopsy findings were consistent with CAD. The lungs were normal in size and weight, but on histopathologic review (Fig), alveolar development was limited and patchy, and intrapulmonary surface area for gas exchange was also limited. This was because of the markedly reduced airspace and persistence of immature interalveolar mesenchyme.

Lessons for the Clinician

- This case highlights the importance of suspecting disorders of lung development and congenital surfactant deficiency in infants with severe and refractory respiratory failure.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the stages and mediators of normal and abnormal cellular and structural development of all components of the lung.
- Know the timing of the biochemical maturation of the lung and the physiological and biochemical factors affecting this timing.

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Case 2: Refractory Respiratory Failure and Pneumothorax in a Full-Term Newborn

Benjamin D. Reed, Shreyas Arya, Kevin R. Dufendach and Daniel Leino

NeoReviews 2018;19;e109
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3 Abdominal Distention and Gastrointestinal Bleeding in a Late Preterm Neonate

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AUTHOR DISCLOSURE Drs Raut, Badatya, Thakur, Kumar, and Kler have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A late preterm female neonate is born at 34 weeks, 6 days of gestation, with a birthweight of 2.1 kg. The mother is a gravida 2 woman and the infant is delivered via cesarean section in view of scar dehiscence. The infant cries immediately after birth and does not require any resuscitation. She develops respiratory distress in the delivery room, is transferred to the NICU, and given continuous positive airway pressure (CPAP). She is comfortable with CPAP and is gradually weaned to room air 48 hours after birth. On the third day after birth, tube feeding is commenced at 20 mL/kg per day. However, the next day she develops abdominal distention, gastrointestinal bleeding, and melena for which feeding is stopped. There is no history of treatment with steroids or nonsteroidal anti-inflammatory drugs. On the same day, she is transferred to a level IIIB NICU for further management.

On admission to the institute, the infant is lethargic and tachypneic. Blood pressure and capillary refilling time are in the normal range. The abdomen is soft without any distention and bowel sounds are present. There is no fresh gastrointestinal bleeding or melena. CPAP (positive end-expiratory pressure, −5; fraction of inspired oxygen, 21%) is restarted for respiratory distress.

CASE PROGRESSION

The infant is given nothing by mouth (*nil per os*; NPO) and total parenteral nutrition. Empirical antibiotic treatment (intravenous meropenem) is started after performing sepsis screening; laboratory testing for platelet count, prothrombin time, and activated partial thromboplastin time; and cultures of blood, cerebrospinal fluid, and urine. Arterial blood gas shows a pH of 7.21, bicarbonate of 14.4 mEq/L (14.4 mmol/L), and anion gap of 22, suggesting increased anion gap metabolic acidosis. Radiograph of the chest is normal but that of the abdomen suggests the presence of gas in the wall of the stomach (Fig 1). The total leukocyte count is 3,800/μL (3.8×10^9/L), C-reactive protein is 68.5 mg/L (652.4 nmol/L), and prothrombin time, activated partial thromboplastin time, and platelet counts are in the normal range. Blood culture yields gram-negative bacteria, *Achromobacter xylosoxidans*, for which modified antibiotics are administered. The opinion of pediatric surgery is obtained, and the treating team and radiologist agree to treat her for isolated gastric pneumatosis without any bowel involvement. She is weaned to room air 36 hours after admission. Repeat radiography performed on days 7 and 10 after admission shows the resolution of pneumatosis (Figs 2 and 3). The infant continues to remain NPO for 10 days and starts receiving small

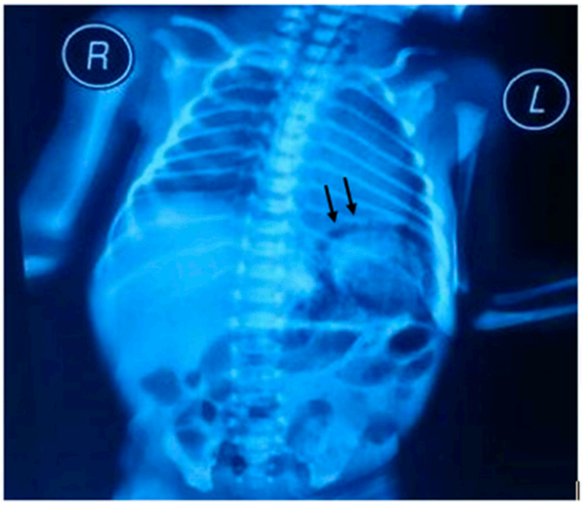

Figure 1. Radiograph of the abdomen on day of admission showing isolated gastric pneumatosis (black arrows).

feedings of 20 mL/kg per day on day 11 of admission. Feedings are gradually increased and she reaches a full feed of 150 mL/kg per day on day 18. For gram-negative bacterial sepsis, she is treated with antibiotics for 14 days and discharged 20 days after birth.

DISCUSSION

Isolated gastric pneumatosis in a neonate is very rare and only a few cases have been reported. Pneumatosis is defined as the presence of gas in the bowel wall. (1) However, it can involve any part of the gastrointestinal tract. Most cases of gastric pneumatosis are caused by obstruction of the proximal bowel because of pyloric stenosis, pyloric atresia, or duodenal web. (2)(3)

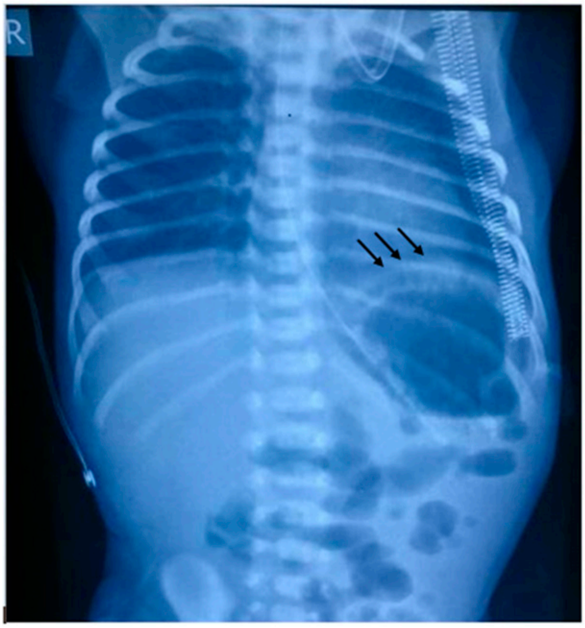

Figure 2. Radiograph of the abdomen on day 7 of admission showing partial resolution of gastric pneumatosis (black arrows).

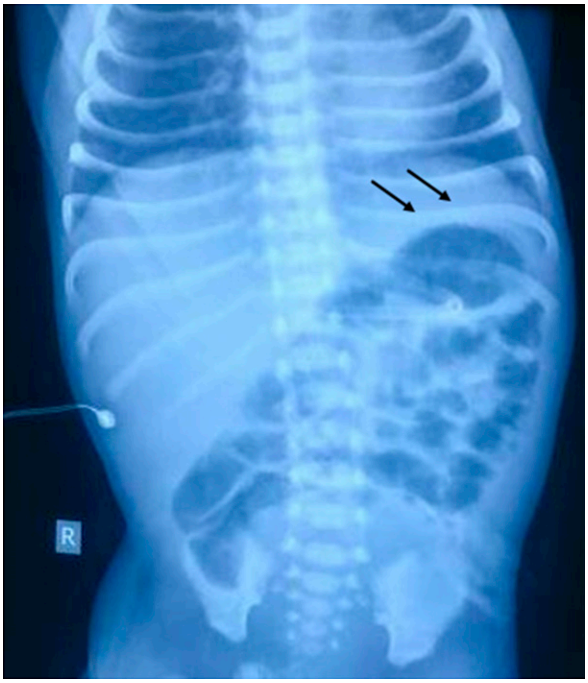

Figure 3. Radiograph of the abdomen on day 10 of admission showing complete resolution of gastric pneumatosis (black arrows).

Gastric pneumatosis is of 2 types—gastric emphysema or emphysematous gastritis. Whenever intraluminal pressure is increased because of proximal bowel obstruction, the intraluminal gas dissects through the intact gastric mucosa and produces linear or cystic pneumatosis. (4) This is known as *gastric emphysema*. It has a good prognosis and these patients improve quickly once the obstruction is relieved. (5) Emphysematous gastritis has a more indolent course because of an infection or inflammation that causes a breach in the gastric mucosa, which is followed by gas entering the mucosa. It has a poorer prognosis and these patients usually take longer to recover. Management is usually conservative with the treatment of underlying infection/inflammation, but surgical exploration may be needed in the presence of pneumoperitonium or suspicion of gangrene. (6) In the current case, there was no proximal bowel obstruction. Presence of gastrointestinal bleeding, metabolic acidosis, classic radiographic findings, normal coagulation profile, and positive blood culture favors the diagnosis of isolated gastric pneumatosis, with late prematurity and sepsis being the predisposing factors.

Lessons for the Clinician

- Usually gastric pneumatosis is associated with fulminant necrotizing enterocolitis or benign etiologies like upper gastrointestinal obstruction or drug exposure.
- Uncommonly gastric pneumatosis can occur in isolation and can present early, with prematurity and sepsis being the predisposing factors.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical manifestations and differential diagnosis of gastrointestinal (GI) bleeding in newborn infants, including the various coagulation disorders that cause GI hemorrhage.
- Know the laboratory and radiographic findings and management of GI bleeding in newborn infants.

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Case 3: Abdominal Distention and Gastrointestinal Bleeding in a Late Preterm Neonate

Bichitrananda Raut, Susanta Kumar Badatya, Anup Thakur, Vijay Kumar and Neelam Kler

NeoReviews 2018;19;e112

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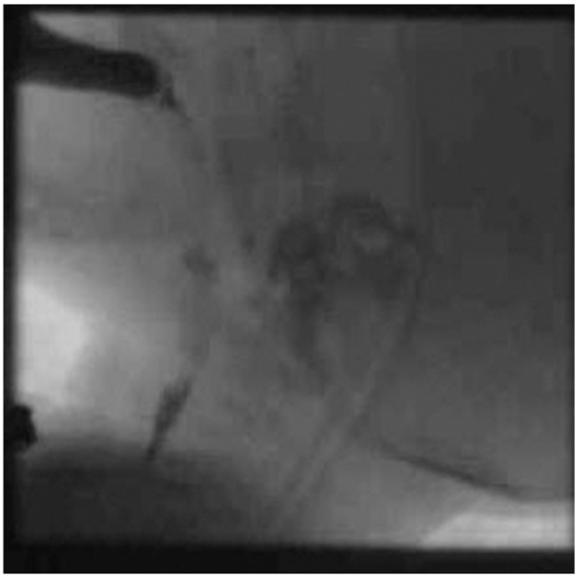
Swallow Studies in Preterm Infants: Indications and Interpretation

Kathryn Davidson, MS, CCC-SLP, BCS-S,* Kayla Hernandez, MS, CCC-SLP, BCS-S*

*Harvard University, Cambridge, MA

CASE

Please view the video clip (Video 1) showing the results of a videofluoroscopic swallow study (also known as a modified barium swallow study).



Video 1. Click here to view the video.

The most likely clinical scenario of the infant in this video is a:

A. Former 29-week preterm infant with a postmenstrual age of 41 weeks who is currently receiving continuous positive airway pressure

B. Former 33-week preterm infant with a postmenstrual age of 42 weeks with desaturations with feeding and requiring supplemental oxygen

C. Late preterm infant with Prader-Willi syndrome now at 43 weeks who is not yet rooting or maintaining an awake state for feeding

D. Term infant who sputters with a fast flow nipple

CRITIQUE

The videofluoroscopic swallow study (VFSS), also known as a *modified barium swallow study*, is a form of instrumental assessment of swallow function. It is conducted in the radiology department by a speech-language pathologist in collaboration with a radiologist; thus, the patient needs to be stable to allow transfer to this location. The infant's caregivers and nurse may also be present

AUTHOR DISCLOSURE Mss Davidson and Hernandez have disclosed no financial relationships relevant to this article. Mss Davidson and Hernandez's current affiliation is Department of Otolaryngology and Communication Enhancement, Boston Children's Hospital, Boston, MA. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Video 2. Click here to view the video.

and often participate in the study by feeding the infant. The following video clip (Video 2) is an example of a "normal" study, demonstrating adequate integration of the suck-swallow-breathe pattern, with 1 suck per swallow, timely swallow onset, and intact airway protection from above; anatomical markers are shown in Fig 1.

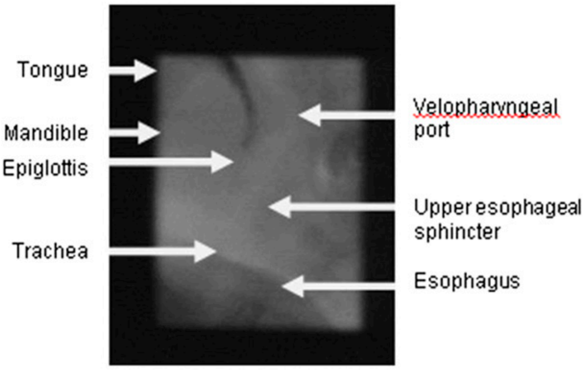


Figure 1. Lateral view with anatomical markers.

There are 3 primary purposes for performing a VFSS:

1. Defining the nature and pathophysiology of a swallowing impairment
2. Provoking the swallowing system to try to demonstrate the dysphagia complaint (eg, ensuring that the end of a feeding is documented by fluoroscopy in a patient who consistently exhibits difficulty near the end of a feeding)

TABLE. Considerations for Determining Appropriateness of Videofluoroscopic Swallow Study (VFSS) in a Neonate

Postmenstrual age	Patients younger than 38 weeks' postmenstrual age may not be demonstrating developmental readiness for full oral feedings. Waiting 1–2 weeks for additional maturation while implementing feeding interventions to improve coordination could successfully avoid radiation exposure.
Physiologic stability and respiratory status	Infants must maintain a calm/awake state for oral feeding. Infants should be weaned to room air or low-flow nasal cannula, because feeding while receiving continuous positive airway pressure significantly increases the risk of laryngeal penetration (ie, material entering the upper airway but remaining superior to the level of the true vocal folds and exiting with completion of the swallow) and aspiration events (Ferrara et al, 2017).
Comorbidities	Infants with multiple comorbidities are at increased risk for difficulties with oral feeding progression (Jadcherla et al, 2010; Dodrill et al, 2008). Patients with chronic respiratory disease, neurologic injury, airway anomalies, congenital heart disease, etc. have a higher risk of aspiration and therefore, clinicians should have a lower threshold for seeking VFSS with these populations.
Response to interventions at the bedside	The following therapeutic interventions improve coordination of the suck-swallow-breathe pattern and may alleviate need for instrumental assessment with radiation exposure: • *Positioning*: Swaddling an infant in a flexed body position optimizes his/her organization and neural alignment for overall stability during feeding (Clark et al, 2007; Thoyre et al, 2012). Transitioning the infant to an elevated side-lying position promotes greater physiologic stability with improved bolus management for self-regulated breathing and less variability in oxygen saturation, heart rate, and respiratory rate (Thoyre et al, 2012; Clark et al, 2007). • *Flow Rate*: Slower flow nipples improve physiologic stability during feeding and optimize integration of respiration and swallowing (Chang et al, 2007; Ross and Brown, 2002). • *External Pacing*: Pacing refers to either tilting the nipple toward the palate to cease the flow of liquid or removing the nipple from the infant's mouth entirely. This provides external support for integration of respiration and improves the infant's endurance and physiologic stability (Law-Morstatt et al, 2003).

3. Identifying compensatory strategies to facilitate the patient's best performance so that a management protocol can be developed (Benson and Tuchmann D, 1994).

Although aspiration may be captured by a VFSS, it is important to understand that the presence or absence of aspiration is not the sole purpose of a VFSS. There are many considerations for determining whether a patient is an appropriate candidate for a VFSS including, but not limited to, postmenstrual age, physiologic stability, respiratory status, and comorbidities (Table). In addition, many feeding interventions made at the bedside can successfully improve coordination of the suck-swallow-breathe pattern and should generally be tried first before seeking VFSS.

The patient in the case (Video 1) presents with an immature suck-swallow-breathe pattern, resulting in eventual aspiration of thin liquid via a standard flow nipple; this aspiration is shown in Fig 2. This patient's coordination improved significantly with a slower flow rate (ie, Dr. Brown's preemie flow), with no further episodes of laryngeal penetration or aspiration. This case demonstrates the need to assess for change in swallow function over time, because most preterm infants exhibit worsening coordination as the feeding progresses, resulting in higher risk of bolus misdirection. Use of a slower flow nipple in this case eliminates the need for thickening, which comes with associated risk factors including gastrointestinal issues (eg, increased risk for necrotizing enterocolitis for some types of thickening agents, constipation, changing nutritional composition), poor endurance, and variability in viscosity. This infant can achieve full oral feedings using the preemie flow nipple and may be appropriate for clinical advancement as he matures, with consideration of repeat VFSS should any signs or symptoms concerning for aspiration emerge.

Video 3 shows an infant with more severe oropharyngeal dysphagia characterized by discoordination of the nutritive sucking pattern and gross, silent aspiration with both thin and thickened liquids. Interventions completed at the bedside, including positional adjustments, slower flow rates, and external pacing, did not resolve the infant's apneic and bradycardic events. Therefore, a trial of thickening was also attempted during the study.

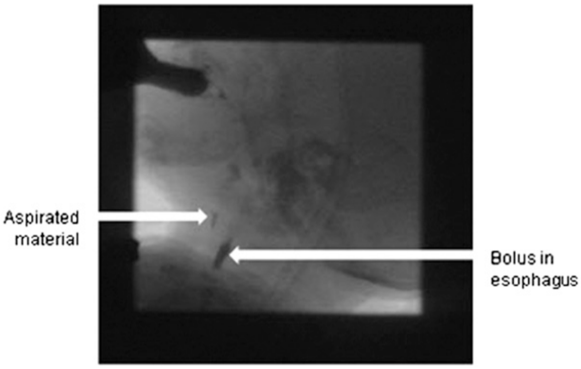
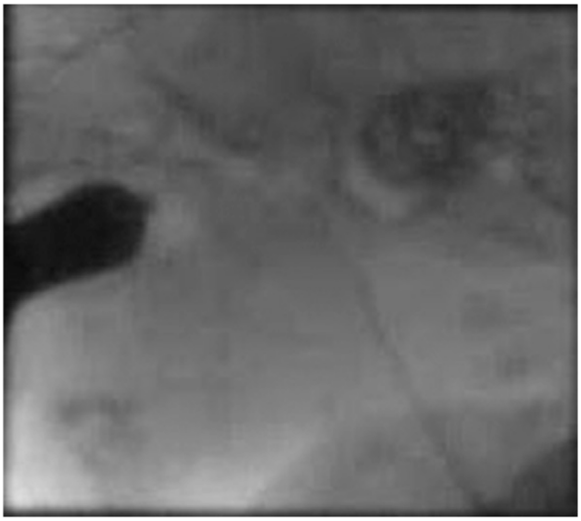


Figure 2. Aspiration with standard flow nipple.



Video 3. Click here to view the video.

Thickened liquids are often tried when other strategies prove unsuccessful because thickening slows the rate of liquid flow and increases sensory input. However, this case emphasizes the importance of gathering instrumental information of swallow function in at-risk neonates rather than implementing empirical trials of thickening. Although this strategy of foregoing a VFSS can be beneficial later in infancy and throughout childhood, most preterm and term newborns with dysphagia aspirate silently (ie, no protective cough response). Empirical thickening would have led to silent aspiration of thickened liquids while also introducing the risks associated with thickening. This patient will require nonoral means of nutrition and would likely benefit from oral stimulation in the interim to maintain interest and prevent oral aversion, which might include use of a dry pacifier or pacifier dips during bolus nasogastric feedings.

CORRECT RESPONSE

B. Former 33-week preterm infant with a postmenstrual age of 42 weeks with desaturations with feeding and requiring supplemental oxygen.

Suggested Readings

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Preeclampsia with Severe Features and Acute Abruption

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal values for arterial umbilical cord gas values and indications of acidosis are defined in the Table.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

AUTHOR DISCLOSURE Dr Grable has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. Arterial Umbilical Cord Gas Values

	pH	Pco_2 (mm Hg)	Po_2 (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤−10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤−10
Metabolic acidosis	<7.20	<60	Variable	≥−10
Mixed acidosis	<7.20	>60	Variable	≥−10

*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695.

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable
Minimal: Amplitude range is greater than undetectable to 5 beats/min
Moderate: Amplitude range is 6–25 beats/min
Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
    - ○ Normal: ≤5 contractions in 10 minutes
    - ○ Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
    - – Baseline rate: 110 to 160 beats/min
    - – Baseline FHR variability: Moderate
    - – Late or variable decelerations: Absent
    - – Early decelerations: Present or absent
    - – Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
    - – Bradycardia not accompanied by absent variability
    - – Tachycardia
    - – Minimal or marked baseline variability
    - – Absent variability without recurrent decelerations

  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline
- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - ■ Recurrent late decelerations
    - ■ Recurrent variable decelerations
    - ■ Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum FHR monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

A 40-year-old gravida 1, para 0 woman presented to the labor and delivery (L&D) department at 28-1/7 weeks of gestation (dated by a 7-week ultrasound scan) with uterine cramping. The cramping began 3 days earlier and had become more painful. She denied vaginal bleeding or leaking fluid. She had no headache, visual changes, or epigastric pain.

She had a medical history significant for a uterine fibroid. Her surgical history was significant only for a breast excisional biopsy without complication. She was active and worked as a physical therapist. She denied smoking, drinking, and recreational drugs. Her medications included only prenatal vitamins.

Her pregnancy was significant for a large lower uterine segment fibroid measuring 16 cm at 18 weeks' gestation. She had an episode of vaginal bleeding at 14 weeks. She underwent level II ultrasonography, which demonstrated normal growth and an echogenic focus in the left ventricle. She is Filipino and because this is a common finding in Asian populations, the echogenic focus was considered a normal variant. However, the patient was offered a noninvasive prenatal screen (cell-free fetal DNA) and amniocentesis and declined both. At the time of the level II ultrasonography, the fibroid measured 17 cm and appeared to be obstructing the lower uterine segment. At 21 weeks' gestation, she presented to L&D feeling pressure and contractions every 2 minutes. She was dehydrated and had a closed cervix. She was treated with intravenous fluids and discharged from the hospital. She failed her 1-hour glucose challenge test, but underwent a 3-hour glucose tolerance test, findings of which were normal (serum glucose, 78 mg/dL [4.3 mmol/L], 180 mg/dL [10 mmol/L], 119 mg/dL [6.6 mmol/L], and 121 mg/dL [6.7 mmol/L]).

On arrival at L&D at 28 1/7 weeks' gestation, her initial blood pressure was 184/94 mm Hg with a heart rate of 68 beats/min, and a temperature of 98.9°F (37.2°C). A repeat blood pressure 7 minutes later was 170/89 mm Hg. She was complaining of sharp uterine cramping, progressively worsening to an intolerable level, with a current pain score of 9/10. At the time of presentation, the fetal heart tones appeared to be recovering from a deceleration. The baseline heart rate was 165 beats/min. The initial FHR tracing is shown in Fig 1.

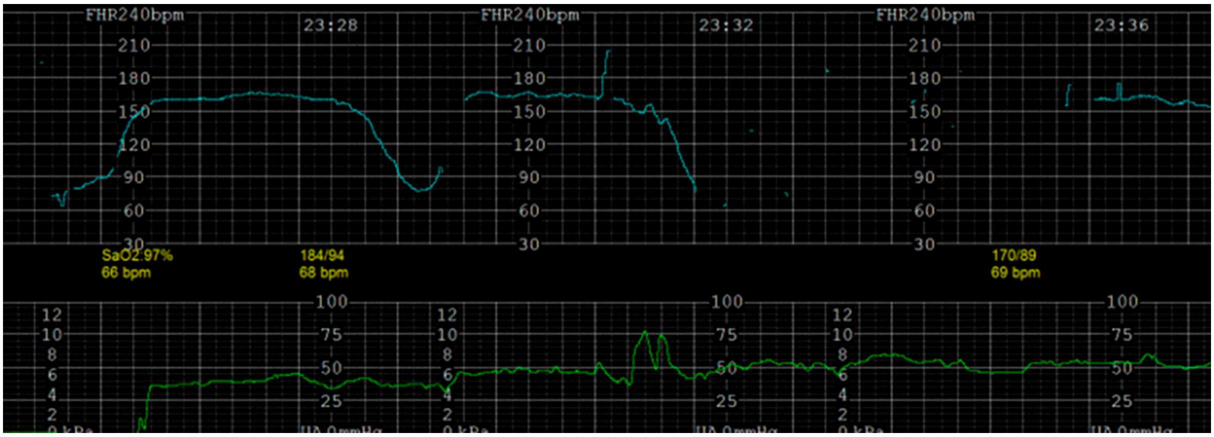

Figure 1. Electronic fetal monitoring strip 1.

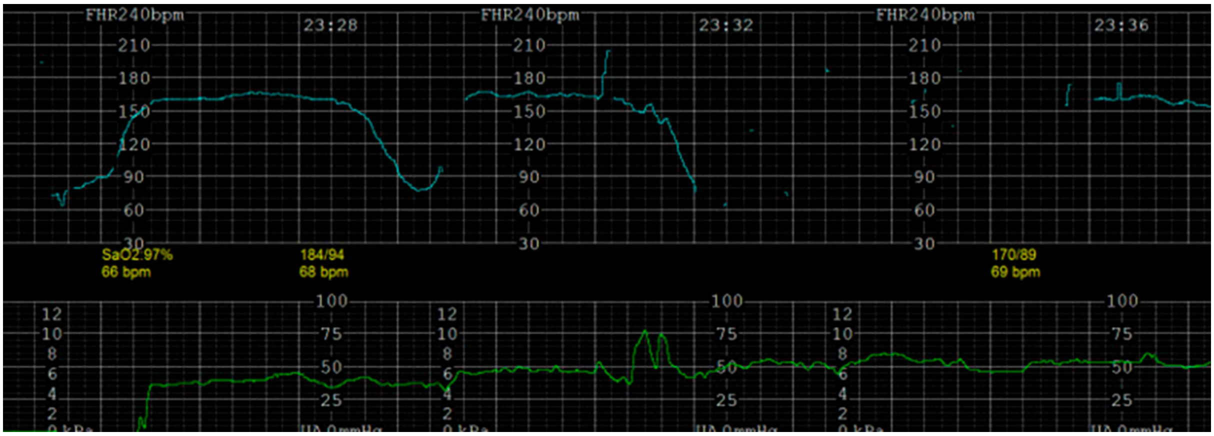

Figure 1. Electronic fetal monitoring strip 1.

Findings on EFM strip 1 are as follows:

- Variability: Minimal
- Baseline rate: 165 beats/min
- Episodic pattern: Recurrent variable decelerations
- Periodic pattern: None
- Uterine contractions: Irritability
- Interpretation: Category II, however difficult to interpret given areas of discontinuous tracing (1)
- Differential diagnosis: Placental abruption, cord prolapse, placental insufficiency, preeclampsia, intrauterine growth restriction, oligohydramnios, vasa previa/velamentous cord insertion
- Action: Obtain intravenous access, perform bedside ultrasonography and internal examination, evaluate for preeclampsia, notify maternal-fetal medicine

On examination, her cervix was 2-cm dilated, 50% effaced, and high. There was no evidence of ruptured membranes or cord prolapse. Bedside ultrasonography demonstrated the fetus to be in breech presentation with normal amniotic fluid. The fibroid was again identified. The scan was limited because of the size of the fibroid. Intravenous access was obtained. She had laboratory screening to rule out preeclampsia as a result of the severe range blood pressures and new-onset hypertension. Anesthesia and maternal-fetal medicine were notified. The continued FHR tracing is shown in Fig 2.

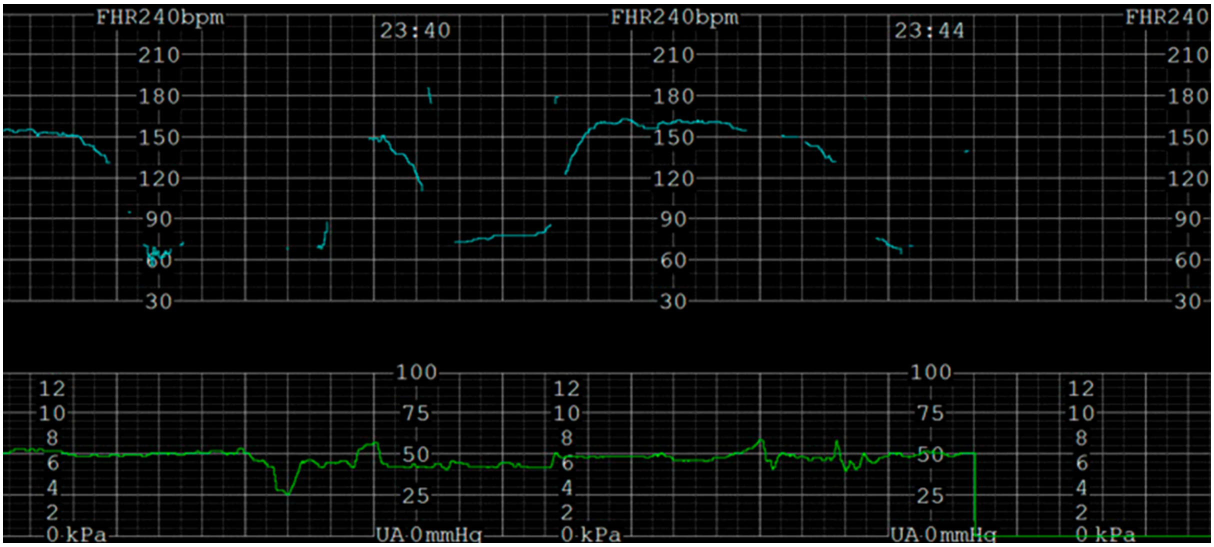

Figure 2. Electronic fetal monitoring strip 2.

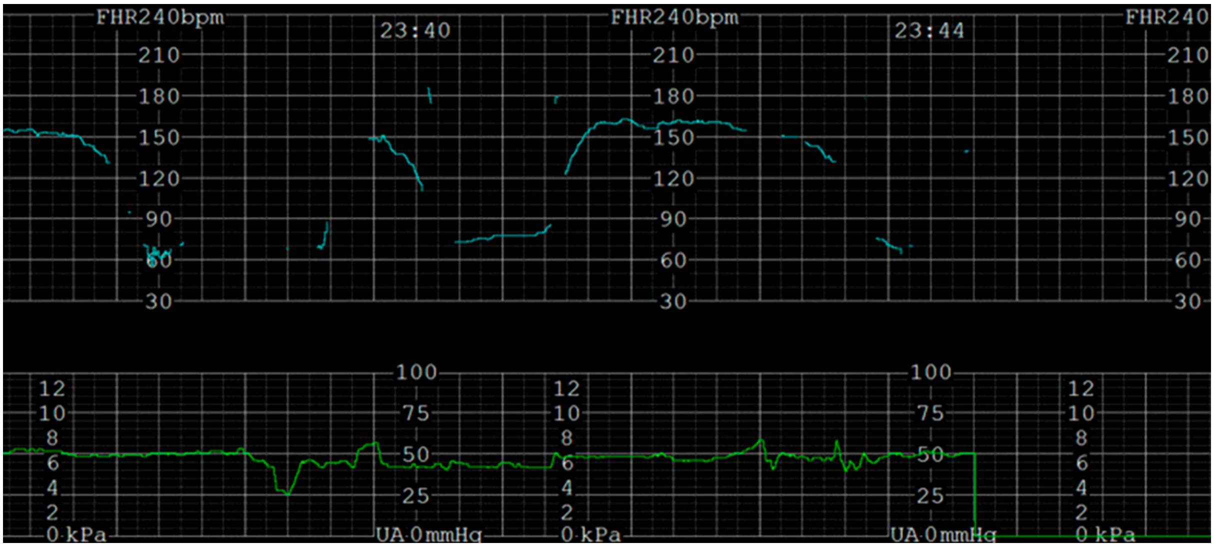

Figure 2. Electronic fetal monitoring strip 2.

Findings on EFM strip 2 are as follows:

- Variability: Minimal
- Baseline rate: 160 beats/min
- Episodic pattern: Recurrent variable decelerations
- Periodic pattern: Prolonged decelerations
- Uterine contractions: Irritability
- Interpretation: Category II. Although the tracing is interpreted as a category II tracing, areas of discontinuous tracing are audible as prolonged decelerations
- Differential diagnosis: Placental abruption, preeclampsia, placental insufficiency
- Action: Consider urgent delivery

Given a likely diagnosis of placental abruption in the setting of contractions, severe range hypertension/possible preeclampsia, and recurrent FHR decelerations, the decision was made to proceed with an urgent cesarean section. The benefit of waiting for laboratory results and observing the FHR for improvement was outweighed by the risks of continuing the pregnancy. Intravenous medication was not provided for blood pressure control at this time because of the expected need for general anesthesia and risk of intraoperative hypotension. The patient was transferred to the operating room. Before being prepared for surgery, a final brief FHR tracing was obtained, which is shown in Fig 3.

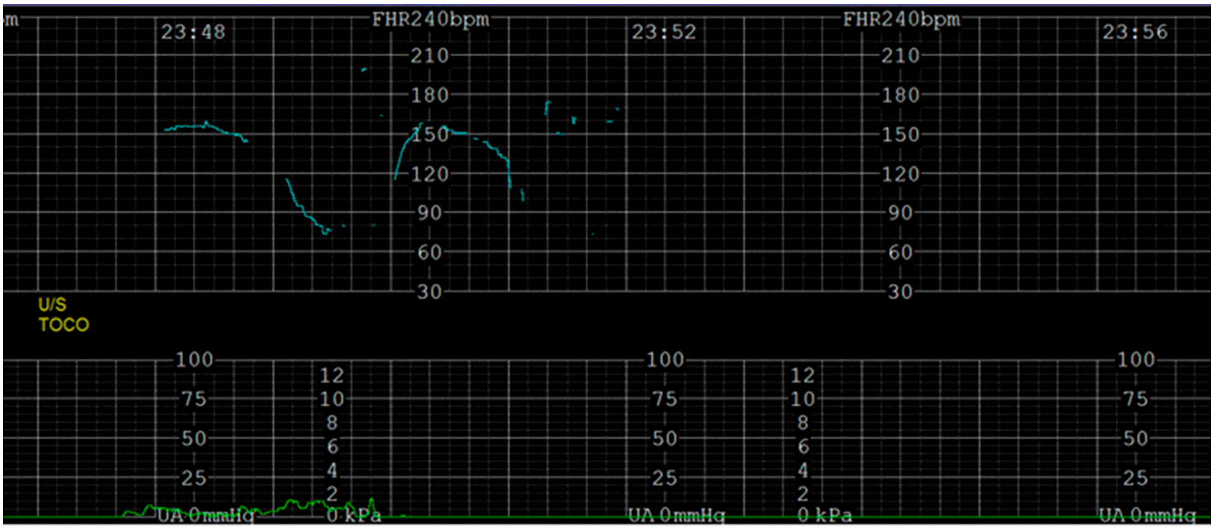

Figure 3. Electronic fetal monitoring strip 3.

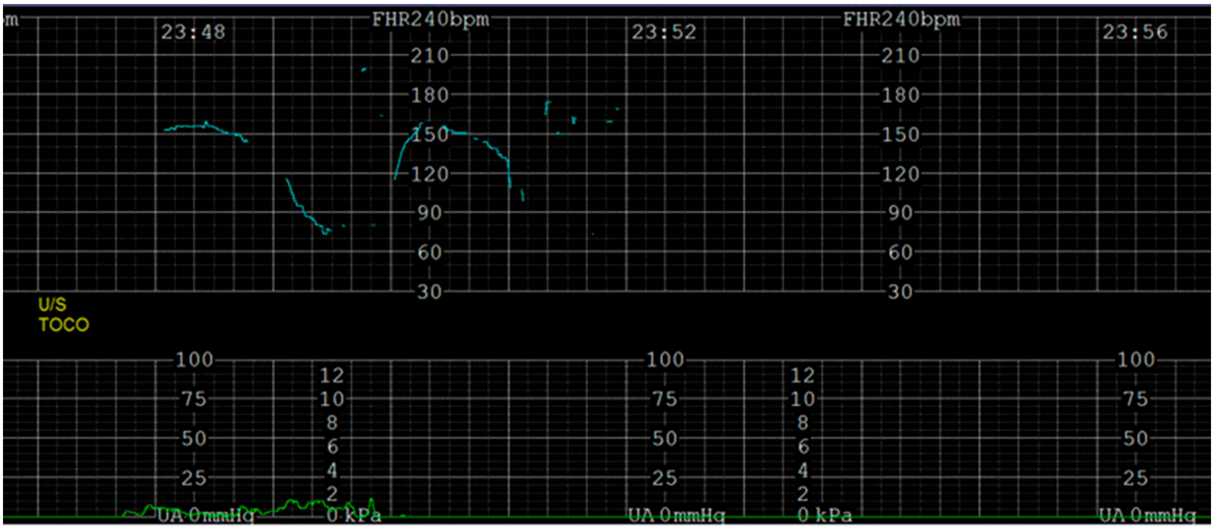

Figure 3. Electronic fetal monitoring strip 3.

Findings on EFM strip 3 are as follows:

- Variability: Minimal
- Baseline rate: Likely 155 beats/min, but unable to be determined given the short FHR tracing
- Episodic pattern: Recurrent variable decelerations
- Period pattern: None
- Uterine contractions: Not measured
- Interpretation: Category II with areas of discontinuous tracing
- Differential diagnosis: Placental abruption, preeclampsia
- Action: Due to continued recurrent decelerations, proceed with urgent cesarean delivery

OUTCOME

The patient initially presented to L&D at 11:20 pm. The initial external fetal monitor was placed at 11:26 pm. At 11:43 pm, the patient was transferred to the operating room for urgent delivery. After reevaluation of the FHR in the operating room, the patient was prepared for surgery. General anesthesia was initiated at 11:55 pm and a 600-g viable female infant was delivered at 11:56 pm through an uncomplicated low transverse cesarean delivery (13 minutes after transfer to the operating room). A placental abruption was noted with evidence of bloody amniotic fluid and clots adherent to a small-appearing placenta. Quantified blood loss was 1,115 mL. Umbilical cord gases could not be obtained because of insufficient cord blood. Results of the laboratory testing for preeclampsia were available after surgery and were consistent with preeclampsia with severe features based on blood pressure and proteinuria. The protein-creatinine ratio was 14.93 (normal <0.30) and the remainder of the laboratory test results were normal.

She received no antihypertensive medication before delivery. Due to general anesthesia and the delivery itself, there was an initial significant improvement in her blood pressure intraoperatively and after delivery. The patient received magnesium for seizure prophylaxis for 24 hours. However, with increasing blood pressures on postpartum day 1, she received extended-release nifedipine 60 mg daily for blood pressure control. Of note, antihypertensive drugs were discontinued by 4 weeks after delivery.

Placental pathology demonstrated a 120-g placenta, which is small for gestational age (SGA; normal 210–331 g). Findings were consistent with severe maternal vascular malperfusion with villous infarcts (the largest of which measured 5.5 cm in greatest diameter and occupied 30% of the parenchyma), with accelerated diffuse villous maturation and decidual vascular thrombi.

In addition, a small chorangioma (0.6 cm in greatest dimension), focal chronic villitis, and paramarginal insertion of the umbilical cord were noted.

After delivery, the infant's heart rate was normal, but she had apnea with poor tone. The neonatology team was present and immediately started positive pressure ventilation (PPV). She initially made only intermittent gasps and small crying efforts. Given steady improvement, PPV was discontinued at 4 minutes of age and she made a transition to continuous positive airway pressure +5 mm Hg. During the resuscitation, the fraction of inspired oxygen was initially 0.40, which increased to 0.80, and then decreased to 0.50. The infant's Apgar scores were 3 at 1 minute, 5 at 5 minutes, and 7 at 10 minutes.

The infant's birthweight was 600 g, which is the 4th percentile (Z= −1.78) based on Fenton weight-for-age data. The height was 29 cm, which is less than the 1st percentile (Z= −2.94) based on Fenton length-for-age data. The head circumference was 21 cm, which is less than the 1st percentile (Z= −2.94) based on Fenton length-for-age data. A urine cytomegalovirus polymerase chain reaction was negative. Thrombocytopenia was noted, likely due to growth restriction, but resolved without transfusion. Head ultrasonography did not show any abnormality. She had respiratory insufficiency requiring intubation, surfactant, and postnatal steroids. She also had multiple bouts of feeding intolerance necessitating prolonged parenteral nutrition, but maintained appropriate growth after delivery. In addition, she had symptomatic bacteremia from *Staphylococcus epidermidis*, which required prolonged antibiotic treatment.

DISCUSSION

Intrauterine growth restriction (IUGR) and preeclampsia are significant causes of maternal and neonatal morbidity and mortality. Preeclampsia affects approximately 2% to 5% of pregnancies. It is also associated with a 4-fold increase in the risk of IUGR, which may be associated with long-term neonatal complications. (2)(3) Risk factors for preeclampsia include hypertension, diabetes, renal disease, multiple gestations, obesity, and a history of preeclampsia. While the cause of preeclampsia is unknown, both IUGR and preeclampsia are associated with inadequate placental blood perfusion and ischemia resulting in endothelial dysfunction and platelet and clotting system activation. (2) This may result in catastrophic pregnancy complications, such as abruption and fetal demise.

Stable patients with preeclampsia with severe features are managed expectantly until 34 weeks' gestation to reduce the complications of prematurity. However, affected women may face many potential complications as they work toward the goal of increasing gestational age. There are increased risks of intensive care unit admission; *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelets counts (HELLP) syndrome; pulmonary edema; eclampsia; abruption; subcapsular liver hematoma; stroke; stillbirth; neonatal death; and perinatal asphyxia. The risk of abruption in a review of patients of less than 34 weeks' gestation who received expectant management was 5.1% (2.2%–8.5%). In the same study, more than 30% of infants were SGA. (4)

A placental abruption is defined as a premature separation of the implanted placenta before delivery of the fetus. (5) It occurs on average in 1 in 200 deliveries and contributes significantly to maternal and neonatal morbidity and mortality. Although multiple risk factors exist, the most common cause is maternal hypertensive disorders, which occur in 44% of cases. Maternal trauma, including a motor vehicle accident, falls, and assaults, is associated with 1.5% to 9.4% of cases. Cigarette smoking, drug use, premature rupture of membranes, twin gestation, chorioamnionitis, advanced maternal age, elevated maternal serum α-fetoprotein, bleeding in the second trimester, uterine fibroids, and a history of abruption are all associated risk factors. The risk of recurrence of abruption is 4% to 12% after 1 pregnancy and 25% after 2 consecutive pregnancies complicated by abruptions. (6)

Fetal and neonatal morbidity is caused by the severity of the abruption itself and the potential complications of prematurity. Delivery is required when there is maternal bleeding that is not resolving and causing maternal shock or recurrent FHR decelerations that are a sign of inadequate placental perfusion. Expectant management may be possible in the setting of a marginal or partial abruption. However, with a complete abruption, an expedited delivery is necessary. Potential maternal complications of an emergency cesarean section include disseminated intravascular coagulation, postpartum hemorrhage, and hysterectomy.

In a case of category III FHR tracing that does not resolve, a prompt delivery should be considered. However, with a category II FHR tracing, the recommendation is for surveillance and implementation of intrauterine resuscitative measures as indicated. These may include lateral positioning, oxygen, intravenous fluids, discontinuation of oxytocin, administration of tocolytic medications such as terbutaline, and amnioinfusion. However, when the cause of the category II tracing does not resolve, and the tracing does not improve, a decision to proceed with delivery must be considered. If the FHR tracing is highly likely to proceed to a category III tracing in a short amount of time, and if the cause of the abnormality cannot be resolved, delivery is indicated to maximize the chance of a successful outcome. Both a cord prolapse and a complete abruption are 2 examples of clinical scenarios in which there may be a category II FHR tracing, but an urgent delivery is indicated. (7)

This patient was unaware that her symptoms of cramping could be associated with both preeclampsia with severe features and an FHR tracing with recurrent FHR decelerations. She had no change in fetal movement and no significant symptoms of preeclampsia. However, she had multiple risk factors for preeclampsia including advanced maternal age, primigravida, and SGA growth. In addition to these risk factors, there were also other possible causes of SGA growth including a small placenta, placental infarcts on placental pathology, and a large fibroid. Together, the risk for placental abruption was significant. The FHR tracing was an effective tool in determining the status of the fetus and need for an urgent cesarean delivery.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effects on the fetus and/or newborn infant of severe preeclampsia, including HELLP syndrome, and its management.
- Know the diagnosis and management of maternal/fetal blood loss such as placenta previa, placenta abruption, vasa previa, and maternal-fetal hemorrhage.

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ANSWER KEY FOR FEBRUARY 2018 NEOREVIEWS

Evidence for Role of Genital Mycoplasmas in Preterm Birth and Neonatal Lung Injury: 1. D; 2. E; 3. C; 4. A; 5. B.

A Focus on Microbiome Completeness and Optimized Colonization Resistance in Neonatology: 1. B; 2. C; 3. C; 4. A; 5. B.

Strip of the Month: Preeclampsia with Severe Features and Acute Abruption

Ian Grable

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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A Unique Case of Facial Dysmorphism in an Infant

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THE CASE

A preterm infant with a ventricular septal defect and facial dysmorphisms.

Prenatal and Birth Histories

- Born to a 21-year-old gravida 2, para 2 woman with a healthy prior child.
- The pregnancy was complicated by an abnormal quadruple screen (with an elevated α-fetoprotein) and fetal cardiac ultrasonography that showed concerns for tetralogy of Fallot and persistent oligohydramnios of uncertain etiology. There was no evidence of growth restriction.
- Estimated gestational age: 32 6/7 weeks.
- An emergency cesarean delivery was performed because of premature labor and concerns for placental abruption.
- Apgar scores: 8 and 9 at 1 and 5 minutes, respectively.

Presentation

After birth, the infant was admitted to the NICU because of prematurity. He required supplemental oxygen through a nasal cannula for a brief period (<1 week) and was successfully weaned to room air. Echocardiography revealed a large perimembranous ventricular septal defect (VSD) with 2 small ventricular muscular defects. The team identified facial dysmorphisms and ordered a microarray analysis.

Physical Examination (After Birth)

- Birthweight: 1.57 kg (27th percentile), length: 41 cm (34th percentile)
- Head circumference: 28 cm (17th percentile)
- Heart rate: 150 beats/min
- Respiratory rate: 76 breaths/min
- Blood pressure: 55/33 mm Hg (mean arterial pressure 40 mm Hg)
- Oxygen saturation: 89% (in room air)
- Head: Small head circumference; normal, open, flat fontanelles; no cranial molding; almond-shaped eyes, epicanthal folds, hypertelorism, flat nasal bridge, low-set ears, thin upper lip, and micrognathia (Figs 1 and 2); red reflex was present bilaterally; intact palate
- Lungs: Coarse breath sounds bilaterally; tachypnea; no other signs of respiratory distress
- Cardiovascular: Normal S1 and S2 with 3/6 harsh holosystolic murmur loudest at the left parasternal border

AUTHOR DISCLOSURE Drs Samuel, Karpawich, and Scheurer-Monaghan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

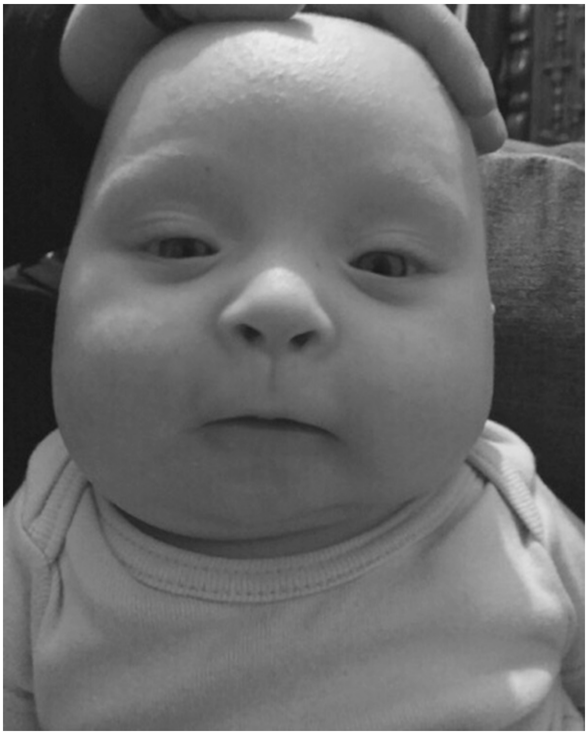

Figure 1. Frontal view of the infant at age 3 months which reveals almond-shaped eyes, epicanthal folds, hypertelorism, a flat nasal bridge, a small head circumference, and a thin upper lip.

- Abdomen: Soft, nontender; no organomegaly; no masses
- Genitourinary: Bilateral hydroceles, patent anus
- Skin: No jaundice, no rash

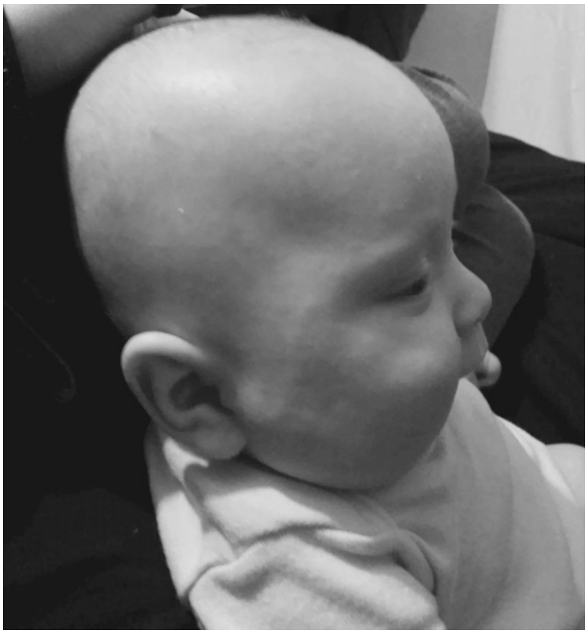

Figure 2. Side view of the infant's face at age 3 months showing micrognathia and low-set ears.

- Musculoskeletal: Spine appears normal; no limb abnormalities
- Neurologic: Increased tone in upper extremities; symmetric Moro reflex, normal suck reflex

PROGRESSION

The infant had a 2-month NICU hospitalization complicated by congestive heart failure secondary to the large VSD, which was associated with poor weight gain. At 2½ months of age, the VSD was surgically repaired with a complicated postoperative course as a result of a methicillin-sensitive *Staphylococcus aureus* infection, which was treated with antibiotic therapy for 6 weeks. The infant had a postoperative pericardial effusion that required drainage. Following the VSD repair, his growth improved. He developed bilateral inguinal hernias that were surgically repaired at 3 months of age. During the hospital course, the infant was found to have increased tone in the upper extremities and magnetic resonance imaging was performed, which showed delayed myelination consistent with prematurity. At 4 months of age, the infant exhibited mild gross motor delay.

DIFFERENTIAL DIAGNOSIS

- Cri du chat syndrome (chromosome 5p deletion syndrome)
- Noonan syndrome (multiple gene mutation)
- Prader-Willi syndrome (chromosome 15 segment deletion)
- Rubinstein-Taybi syndrome (chromosome 16p13.3 syndrome)
- Trisomy 18 syndrome
- Trisomy 21 syndrome

ACTUAL DIAGNOSIS

The microarray analysis revealed a duplication of chromosome 16q23.1, which has not been previously reported in the literature.

The duplicated interval involved 3 known genes (*CNTNAP4, LOC101928203, MIR4719*). The assay did not rule out balanced chromosomal abnormalities; imbalances of chromosomal regions that were not represented by probes on the array; or mosaicism. Further genetic testing with fluorescence in situ hybridization and genetic counseling were recommended. However, the parents were noncompliant with that request. Family history did not reveal any other inherited genetic defects.

WHAT THE EXPERTS SAY

To our knowledge, this is the first reported case of chromosome 16q23.1 duplication. The unique feature of chromosome 16 that differentiates it from other chromosomes is its larger than average fraction of repetitive sequences and mutations in which certain pathogenic characteristics may develop. (1) Although chromosome 16 abnormalities are relatively rare in the population, some of the known abnormalities include complete trisomy 16, mosaic trisomy 16, and deletions and duplications of certain segments of the long and short arm of chromosome 16. Trisomy 16 is not compatible with life and is a common cause of miscarriages. (2) An interesting study by Neusser et al concluded that paternal meiotic nondisjunction errors are associated with an increased rate of spontaneous abortion similar to maternal chromosomal disomy. (3)

The features of mosaic trisomy 16 vary greatly but the more common characteristics include intrauterine growth restriction, congenital heart defects, delayed development, intellectual disability, obesity, seizures, and an association with autism. (4)(5) It was initially thought that this mutation is a variant of uncertain clinical significance but later studies found the pathogenic nature of the mutation. Deletion of chromosome 16p11.2 is associated with autism, poor weight gain, microcephaly, and developmental delay, with speech delay being most prominent. (6) Deletion of the 16q24.1 region can lead to alveolar capillary dysplasia, misalignment of the pulmonary veins, and pulmonary hypertension. (7) Translocation of certain segments of chromosome 16 with other chromosomes has been linked to hematologic abnormalities including acute myelogenous leukemia. (8) Rubinstein-Taybi syndrome (also known as *chromosome 16p13.3 syndrome*) is associated with failure to thrive, increased risk of life-threatening infections, intellectual disability, and an association with leukemia and lymphoma. (9) Inversion of chromosome 16 (p13q22) is also thought to be associated with a unique cytogenic subtype of acute myelomonocytic leukemia with a favorable prognosis. (10)

CONCLUSIONS

- Information on chromosome 16 mutations and associated clinical defects is limited. Although certain mutations of chromosome 16 (full trisomy, mosaic trisomy) have been described, in general, the amount of available information is scant.
- This report presents the first case of an infant with chromosome 16q23.1 duplication and describes the unique phenotypic features, congenital heart abnormality, and complications associated with his clinical course. A follow-up evaluation 3 months after birth demonstrated abnormalities of motor development.
- Whether or not this specific mutation is clinically relevant remains a question. The associated facial dysmorphism is most likely the strongest factor that evokes concern of any clinical significance associated with this duplication.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the concepts of insertion, deletion, inversion, and translocation.

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A Unique Case of Facial Dysmorphism in an Infant

Sharmeen Samuel, Peter P. Karpawich and Andrea Scheurer-Monaghan

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Answer Key appears on page e200.

A Missing Piece from the World of Science: Remembering Michael P. Sherman

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Michael P. Sherman, MD, PhD (doctor honoris causa), FAAP (Fig 1), passed away peacefully on September 22, 2017, following complications from a stroke. Michael was a mentor, colleague, and collaborator to many and a respected educator, dedicated scientist, and physician to all. Dr Sherman was a superb neonatologist and world-renowned scientist focusing on infection and immunity in the newborn. He was Professor Emeritus of Child Health, University of Missouri, Columbia, MO, and Professor Emeritus of Pediatrics, University of California, Davis (UC-Davis). Dr Sherman's scientific accomplishments extended over

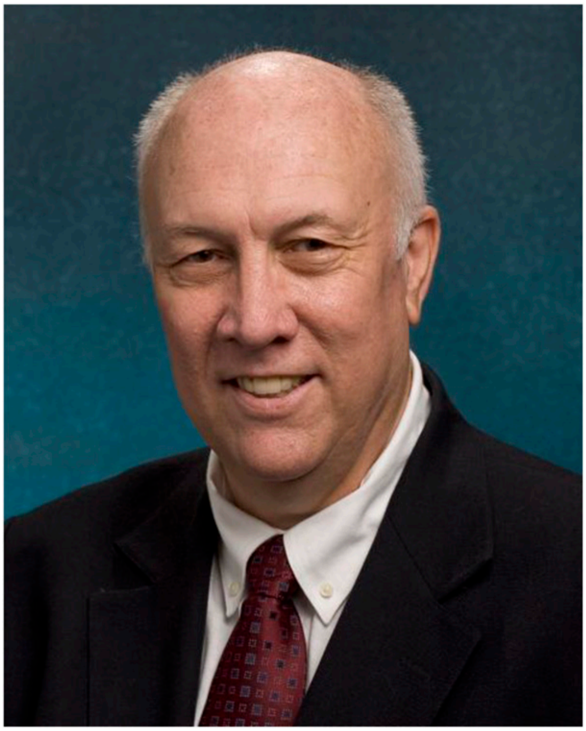

Figure 1. Dr Michael P. Sherman June 8, 1942–September 22, 2017.

AUTHOR DISCLOSURE Drs Wahidi, Reese, and Sherman have disclosed no financial relationships relevant to this article. Dr Underwood is a member of Abbott Laboratories speakers' bureau and a consultant with Avexegen. He also has a research grant with Evolve Bioscience. Dr Niklas is an employee and stockholder of Prolacta Bioscience, Inc. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

decades, with notable contributions in the fields of microbiology, immunology, genetics, and neonatal intensive care. He was born on June 8, 1942. Michael's intellectual reach was enviable, and his passion for understanding and curing disease will be greatly missed.

Dr Sherman attended California State Polytechnic University in San Luis Obispo, CA, and graduated in 1965 as a member of the Beta Beta Beta Honor Society with honors in Microbiology. He was a member of Alpha Omega Alpha National Medical Honor Society and graduated *cum laude* from the Medical College of Wisconsin, Milwaukee, WI (formerly Marquette School of Medicine) in 1969. He completed his pediatric internship and residency at the University of Michigan and was a Senior and Chief Resident in the Department of Pediatrics, University of California San Diego. Michael was particularly proud of his training in San Diego with the late Louis Gluck, MD, and fondly remembered these years by his membership in the "Gluck Club." Michael served as a Major in the Air Force and as the Chief of Pediatric Services at Vandenberg US Air Force Hospital in San Diego, CA, from 1972 to 1974. He completed a fellowship in Neonatal-Perinatal Medicine at UC-Davis in 1976.

THE LUNG, MACROPHAGES, AND NITRIC OXIDE

Michael's career spanned more than 35 years (Fig 2), including service and leadership positions at Kaiser Medical Center in Sacramento, CA, University of California, Los Angeles (UCLA) Medical Center, the University of Kansas School of Medicine, Baylor College of Medicine, UC-Davis Medical Center, Southern Illinois University School of Medicine, and the University of Missouri, among other appointments. Michael joined the faculty at UCLA School of Medicine in 1982. He spoke of his years at UCLA as his most productive and enjoyable in research. His interest in microbiology and immunology led him to focus on the pathogenesis of group B *Streptococcus*, a then frequent cause of pneumonia, sepsis, and death in newborns. Intent on defining the mechanisms for this vulnerability, Michael collaborated with several investigators at UCLA including Dr Boyd Goetzman, Dr Robert I. Lehrer, and Dr Tomas Ganz, identifying defects in oxidative killing by lung macrophages and defects in the release of microbicidal cationic peptides in the lung as critical factors that permitted GBS colonization and infection in the newborn lung. (1)(2)(3) Alongside Dr Henry Gong and Dr Donald P. Tashkin, Dr Sherman found that tobacco and marijuana use had distant effects on pulmonary alveolar macrophages, providing additional insight into the harmful effects of smoking and drug use on defense in the lung. (4) One of Michael's most exciting collaborations was with the 1998 Nobel Laureate, Dr Louis Ignarro at UCLA where Michael focused on the impact of nitric oxide on health and disease in the lung and multiple organ systems. (5) Michael's research was sponsored by numerous National Institutes of Health (NIH) and other research grants during his career at UCLA and beyond.

LARRY DAVIS / Los Angeles Times

Dr. Mike Sherman with a baby in UCLA's intensive care nursery.

Figure 2. Dr Sherman caring for an infant in the NICU at University of California, Los Angeles, 1983 (reprinted with permission from the LA Times).

GUT HOMEOSTASIS AND THE IMPACT OF LACTOFERRIN, A MAJOR WHEY PROTEIN IN BREAST MILK, AND PROBIOTICS

Groundbreaking work with lactoferrin, a major whey protein component found in breast milk, began at UC-Davis in 2001 with Dr Denis R. Headon and Dr Robert A. Shalwitz. Michael's accomplishments in the mucosal immune system in the lung propelled his interests to understand the benefits of lactoferrin in reducing bacteremia and necrotizing enterocolitis (NEC) in the newborn through its actions in the mucosal lining of the gut. Collaborating with Dr Karel Petrak, then at Agennix Corporation, Michael demonstrated the beneficial effects of oral lactoferrin in reducing systemic infection in animal models of bacteremia and NEC in preclinical rat models of disease. (6)(7)(8) This research was the basis for a randomized clinical trial using recombinant human lactoferrin for reducing nosocomial infections and NEC in preterm newborns, which concluded in 2016 with Dr David Adamkin and Dr Victoria Niklas. (9) Michael's subsequent work defined the role of lactoferrin in shaping the intestinal microbiome of preterm newborns and the development of the gut-brain axis. (10)(11)

Michael's interests in neonatal infection and immunity led him to study key cells of the innate immune system (eg, Paneth cells, eosinophils, and basophils) and their role in NEC and other infant diseases and outcomes. (12)(13)(14)(15)(16) His seminal studies in Paneth cell inhibition led to the development of a novel and promising mouse model with significant advantages over previous animal models. (15)(17) His encouragement in the study of the intestinal microbiota and the impact of probiotics on this developing community in newborns led to early studies of probiotics in premature infants and in NEC. (18)(19)

IMPROVING NEONATAL CARE AND EDUCATION IN POLAND

Dr Sherman's career focused on advancing clinical care through research, but he was deeply committed to improving the lives of newborns, infants, and children around the globe. As early as 1981, Michael began work with the Children's Medical Care Foundation (CMCF), which was first established by Dr Stefan P. Wilk with the mission of improving neonatal care in Poland. Throughout the years, Dr Sherman worked closely with Dr Ryszard Lauterbach, Dr Jerzy Szczapa, and Dr Tomasz Szczapa, along with Dr Maria Kornacka and Dr Janusz Bursa, implementing programs to improve education and practice in neonatal medicine. In 2014, Dr Sherman and Dr Szczapa presented an abstract describing transfusion-associated NEC in the NICU in Poland during the Pediatric Academic Societies meeting at Vancouver, British Columbia. Michael's efforts over 28 years were acknowledged by CMCF as critical to the reduction in infant mortality in Poland from 20 in 1,000 to the current level of 4 in 1,000 live births. In 2015, Michael was awarded an honorary doctorate by Poznan University of Medical Sciences, Poznan, Poland, for these contributions to newborn medical care in Poland (Fig 3). (20) Dr Sherman continued to work with Bjoern Martinoff, the current CMCF President, to ensure that advances in neonatal health care and physician education benefitted countries beyond Poland.

Figure 3. Dr Sherman after receiving his honorary doctorate at Poznan University of Medical Sciences, Poznan, Poland, in 2015.

ACADEMIC SERVICE AND ACCOMPLISHMENTS

Dr Sherman witnessed an era of tremendous growth and discovery in the nascent field of neonatology, where he earned board certificate 552 in 1977 (Fig 4). His joy for science and discovery never waned during his fruitful career, nor did his support and enthusiasm for training the next generation of investigators and clinicians. Michael devoted his career to the development of students, medical residents, and postdoctoral and clinical fellows. He served tirelessly as a mentor, neonatal program director, and chief of neonatology. He was a master teacher at the bedside combining his clinical acumen and command of the literature to inspire generations of trainees, many of whom pursued careers in academic medicine and research, and maintained productive research collaborations.

Dr Sherman was an accomplished author with over 100 peer-reviewed publications, 24 book chapters, 100s of abstracts, and national and international presentations. He served extensively as an NIH study section member over a 30-year period, as well as a reviewer for federal and private

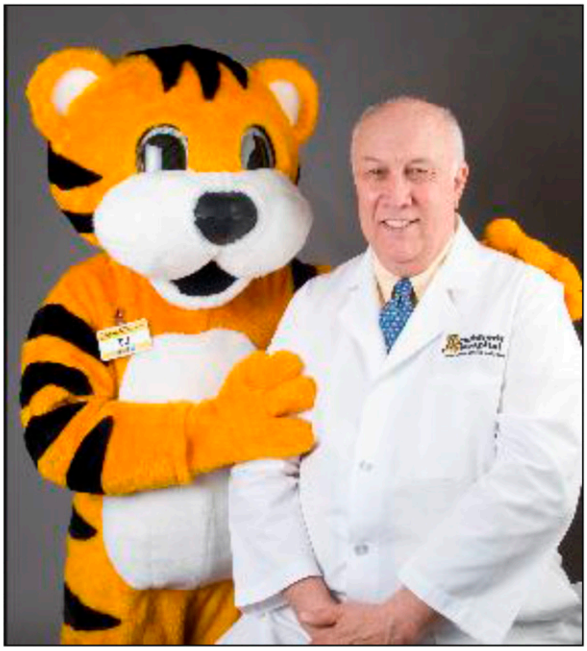

Figure 4. Michael P. Sherman, one of neonatology's unsung heroes.

foundations. He was a member of multiple editorial and review boards with over 40 years of service to the American Academy of Pediatrics, the Section on Perinatal Medicine, and as a member of the Society of Pediatric Research, European Pediatric Research Society, American Pediatric Society, and the Perinatal Research Society.

Dr Sherman is survived by his wife, Dr Jan Sherman; brothers Tom and Tim and sister Kay; sons Michael Jr, Christopher, and Ryan Wheeler; and grandchildren, as well as 5 cats whom he called his 5 daughters. He was predeceased by his parents, Roger and June, as well as his sister, Ruth Ann.

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A Missing Piece from the World of Science: Remembering Michael P. Sherman

Lila S. Wahidi, Jeff Reese, Mark A. Underwood, Jan Sherman and Victoria Niklas

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Understanding the Limitations of Fetal Cardiac Imaging

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Education Gaps

1. Fetal cardiac screening during anatomical surveys and fetal echocardiography may not discern all congenital heart defects.
2. Fetal cardiac screening during anatomical surveys presents challenges with the adoption of newer and more sophisticated imaging recommendations.
3. Fetal echocardiography can aid in the diagnosis of fetal heart disease, but may not be universally available because of clinician unavailability, remote geographical location, and insufficient payer status.

Abstract

Congenital heart defects are among the most common fetal structural malformations, with a prevalence of 8 in 1,000 live births, and are a significant source of infant mortality. Women with low-risk pregnancies are screened for fetal cardiac disease by anatomical ultrasonographic surveys. Fetal echocardiography is typically reserved for pregnant women with a suspected fetal cardiac lesion based on fetal survey and pregnancies at high risk for fetal congenital heart defects. Prenatal diagnosis allows for collaboration and consultation with multiple services, improved recognition of associated extracardiac anomalies, and early detection of underlying genetic anomalies. Theoretically, prenatal diagnosis should offer opportunities to improve postnatal management and long-term outcomes. However, the evidence to suggest benefit to prenatal diagnosis is mixed and the benefit seems to be dependent on the specific cardiac lesion. To facilitate the appropriate utilization of fetal echocardiography, it is necessary to understand how the study is currently being performed, its cost considerations, and how clinicians and sonographers can use it effectively to ensure appropriate image acquisition and interpretation.

Objectives After completing this article, readers should be able to:

1. Recognize the significance of antenatal detection of congenital heart defects on counseling and care coordination.

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ABBREVIATIONS

AIUM	American Institute of Ultrasound Medicine
MFM	maternal-fetal medicine

2. Appreciate the limitations of screening for congenital heart defects based on anatomical surveys and fetal echocardiography.
3. Appreciate the current limitations of universal fetal echocardiography for screening for congenital heart defects.
4. Describe potential solutions to improve fetal cardiac assessment.

BACKGROUND

Congenital heart defects are among of the most common fetal structural malformations, with an estimated prevalence in the United States of 8 in 1,000 live births. The majority of defects occur in pregnancies without risk factors. (1) Approximately 25% of infants with complex congenital heart disease will require some form of neonatal intervention. (2) Congenital heart defects continue to remain a common cause of infant mortality in the developed world. (1) Given the prevalence and burden of disease, recognition and diagnosis are essential to facilitate timely and effective surveillance and therapy.

However, significant barriers prevent fetal diagnosis of cardiac disease. Fetal echocardiography has its limitations; the highest reported detection rates of fetal cardiac abnormalities approach 90% when performed by a pediatric cardiologist. (1)(3)(4) In addition, with expanded indications for fetal echocardiography, changes in recommendations of imaging standards (eg, visualization of outflow tracts), and patient demographics (eg, obesity), the demand and workload has increased for fetal echocardiography. (5)(6) Lastly, the availability of clinicians—from sonographers to physicians—who are capable of capturing and interpreting the imaging studies appropriately is limited, making it difficult for patients from low-resource communities to effectively access and receive appropriate studies. (4)

This review will examine fetal cardiac imaging, its impact on the management of congenital heart defects, the current utilization and impact of fetal echocardiography in the health-care system, and potential strategies to improve access to fetal echocardiography.

CONGENITAL HEART DEFECT IMAGING AND DIAGNOSIS

Most pregnant patients in the United States undergo a screening fetal cardiac examination at approximately 18 to 22 weeks' gestation during the basic anatomy survey. (7) This study is often the only fetal ultrasonography that women experience during their pregnancy. These initial fetal cardiac screens incorporate a series of recommended images outlined in the American Institute of Ultrasound Medicine (AIUM) guidelines that include a 4-chamber view combined with visualization of the outflow tracts. (5) The 4-chamber view alone is able to identify 40% to 60% of congenital heart defects and the addition of the outflow tract views enhances this detection rate to 60% to 90%. (8)(9) More recent work has suggested that the inclusion of other views in the basic anatomy survey may further enhance the screening and diagnosis of congenital heart defects. For example, the 3-vessel view and 3-vessel trachea view provide better imaging of the great arteries, upper venous system, and surrounding anatomy in the upper mediastinum. This additional imaging can help diagnose certain congenital heart defects that would not otherwise be seen on a 4-chamber view, including (but not limited to) transposition of the great arteries, right-sided aortic arch, and left persistent superior vena cava. (10) By combining the 4-chamber, outflow tract, and 3-vessel trachea views, the sensitivity of cardiac disease detection has been reported to be 83.7%. (8) Although these additional views are not currently part of the basic anatomical survey and cardiac screening, they may be added in the future because these views are increasingly being studied and implemented. (11)

Fetuses with suspicious findings on anatomy survey or those who have significant risk factors for congenital heart defects are often referred for further imaging with fetal echocardiography. (12) Fetal echocardiography differs from cardiac screening in that it is designed to identify and confirm cardiac disease. It includes the elements previously mentioned while also including axial views (short and long); long views (aortic arch, ductal arch, and superior and inferior vena cavae); blood flow through systemic veins, pulmonary veins, foramen ovale, atrioventricular valves, and semilunar valves; and long views of the atrial and ventricular septa. (12) The technique to obtain the specified images and expected views of the heart are beyond the scope of this review, but are available in multiple sources.

(7)(12) Although typically performed between 18 and 22 weeks of gestation, fetal echocardiography can be performed as early as the first trimester at 8 to 10 weeks' gestation with adequate success. (13) Clinicians may be either maternal-fetal medicine (MFM) or pediatric cardiology specialists trained specifically in the acquisition and interpretation of these cardiac images. (7)(12)

CONGENITAL HEART DEFECT MANAGEMENT

The goal of the imaging modalities described before is to identify congenital heart disease antenatally and optimize both pre- and postnatal care. In theory, such optimized care can allow for more detailed characterization of the particular lesion, a comprehensive structural survey to identify other structural anomalies, and supplemental genetic testing. (14) In addition, prenatal diagnosis of congenital heart defects provides the opportunity for families to meet with cardiologists, MFM specialists, neonatologists, geneticists, social workers, and nursing staff as needed. (15) Prenatal diagnosis also potentially allows for consideration for fetal cardiac intervention. Fetal cardiac intervention, while promising, remains limited to a small number of very specific lesions at only a handful of centers worldwide. (14)(16)

Overall, it is difficult to determine whether prenatal diagnosis improves neonatal mortality. Some studies have shown substantive impact, whereas others have shown none. (17)(18)(19)(20) A recent meta-analysis evaluating differences in preoperative mortality rates between newborns with and without a prenatal diagnosis found that prenatal diagnosis of specific congenital heart defects (including hypoplastic left heart syndrome, D-transposition of the great arteries, coarctation of the aorta, pulmonary atresia, truncus arteriosus, and critical left heart obstruction with ductal-dependent circulation) led to improved neonatal preoperative survival compared with newborns with a postnatal diagnosis. (21)

Recent articles raise the concern that diagnoses made with fetal echocardiography may not match the postnatal (definitive) diagnosis. (22)(23) In 1 large, single-center study, nearly 10% of patients had a substantially different postnatal diagnosis, which was defined as a change in prenatally planned treatment or the need for unplanned interventions. (23) These discrepancies require acknowledgment of the limitations of ultrasonography and appropriate counseling for parents. (14)(23) Given these limitations, parents should be provided with an estimate of the anticipated postnatal course and reminded that the care plan may need to be modified. (14)(15)(24)(25)

After fetal heart disease is diagnosed prenatally, further imaging to assess for other associated extracardiac anomalies is highly recommended. (5)(26)(27) Previous work has suggested that up to 31% of infants with congenital heart defects have associated extracardiac malformations. (28) Of these, the most frequently seen anomalies were within the nervous system (28%) and gastrointestinal system (22%). Collectively, the combination of congenital heart disease with extracardiac anomalies has been associated with higher rates of neonatal morbidity and mortality. Indeed, mortality rates as high as 70% have been reported in the setting of cardiac and extracardiac anomalies. (26)(27) This combination has a great impact on neonatal outcome, prenatal patient counseling, and management.

Another major factor to consider for appropriate prenatal patient counseling and management is the genetic contribution to congenital heart defects. (28)(29) Genetic testing can yield valuable information in the counseling of patients. Up to 36% of cases of congenital heart defects will have underlying genetic causes, particularly for specific lesions such as atrioventricular septal defects, tetralogy of Fallot, or univentricular heart defects. (28)(29) Fetuses with structural heart disease and a normal karyotype are also less likely to have extracardiac anomalies. In contrast, fetuses with an abnormal karyotype have a higher neonatal mortality rate. (28) Aneuploidy accounts for a significant proportion of genetic abnormalities associated with congenital heart defects, but genetic findings may also be the result of numerous single gene defects and copy number variants. The rapidity of new genetic discoveries and potential associations with congenital heart disease necessitates continual review and updating. (30) Accordingly, the involvement of genetic counselors is imperative in this process. (14)(30)

Understanding the implications of congenital heart defects, extracardiac anomalies, and genetic contribution to disease requires the multidisciplinary collaboration of pediatric cardiologists, MFM specialists, neonatologists, geneticists, social workers, and nursing staff. (14)(15) Although no specific counseling approaches have been shown to be more effective than others, clinicians should expect to review information multiple times with families to ensure an appropriate understanding of the significance and implications of the diagnosis. (15)(25) Whether those options warrant pregnancy termination, referral for in utero therapies, delivery at appropriately resourced facilities, or merely postnatal surveillance, prenatal cardiac diagnosis can be invaluable to affected patients and their families. (21)(29)(31)(32)(33)

Given the importance of prenatal cardiac diagnosis to aid in timely, effective, and appropriate fetal and neonatal care, despite the limitations of imaging, it is critical to investigate new approaches to ensure consistent high-quality care. The demand for effective screening and imaging, as well as appropriate counseling and resources, cannot be overstated.

FETAL ECHOCARDIOGRAPHY UTILIZATION

In recent years, the use of fetal echocardiography has been increasingly studied. (6)(34) With these utilization studies, there has been a refined understanding of the impact that changing recommendations for basic cardiac screening has had on the number of referrals for fetal echocardiography. (6)(34) Moreover, studies examining the cost-effectiveness of the various modalities available for screening as well as the clinicians involved in the performance and interpretation of these tests also demonstrate the impact of fetal echocardiography on the health-care system. (35) These data provide a framework to understand how fetal echocardiography is currently being used and how to address issues with its present use.

A recent publication from a large academic center showed a 200% increase in referrals for fetal echocardiography during a 10-year period (between 2000 and 2010). (6) However, the study also found that the actual prenatal detection rate of congenital heart disease, by percentage of referrals, actually decreased slightly during that time. Referrals were largely driven by suspected congenital heart defects on screening examinations, increased nuchal translucency, and suboptimal imaging. Of those indications, suspected congenital heart disease based on initial screening was most predictive of abnormal fetal echocardiography findings. (6) Interestingly, the referrals after suboptimal imaging increased during this period from 5.2% of all referrals between 2000 and 2002 to 22.3% of all referrals between 2008 and 2010. Suboptimal imaging also had the lowest positive yield at 2.8%, compared with 38.5% for suspected congenital heart disease based on anatomical surveys. These findings suggest that not only is fetal echocardiography being performed more often, but that the overall yield is also decreasing because of referrals for suboptimal imaging. (6)

The drivers for the increase in suboptimal imaging were thought to be the result of 2 issues: 1) maternal body habitus and obesity, and 2) inability to obtain outflow tract imaging during anatomical screening ultrasonography. (6) This second factor was thought to play more of a role because the AIUM recommended that outflow tract imaging be included as part of the anatomical survey during the study period in 2006. (5)(6)(10) Many obstetrical clinicians and sonographers who traditionally had been accustomed to the 4-chamber view may have found the visualization of the left and right ventricular outflow tracts challenging, prompting an increase in referrals for fetal echocardiography. While the diagnosis of total congenital heart defects increased, the positive yield decreased from 8.7% to 7.7% from 2000 to 2010. (6) From a health-care utilization perspective, this lower yield reflects a suboptimal use of fetal echocardiography.

The costs required to obtain such imaging are notable. (35) A recently published cost-effectiveness analysis compared various strategies (4-chamber view vs 4-chamber view with outflow tracts vs nuchal translucency) to evaluate the fetal heart. MFM or non-MFM clinicians (eg, pediatric cardiologists) then evaluated those patients with abnormal findings. Overall, the 4-chamber view with outflow tract visualization as a screening strategy and subsequent referral to MFM for fetal echocardiography produced an average cost per patient of $169.33. This strategy was only marginally less expensive than screening first with the 4-chamber view with outflow tract visualization and subsequent referral to pediatric cardiology ($169.84). Thus, the strategy of using obstetrical clinicians to perform 4-chamber and outflow tract views was found to be the most cost-effective strategy. Although the detection rate of a cardiac defect in the model was slightly different (50% and 63.1% when referred to an MFM specialist and pediatric cardiology, respectively), both proved to be cost-effective strategies. Moreover, the authors evaluated the strategy of simply screening every pregnant woman with fetal echocardiography. They found a greater cost of $513.72 per patient, with a theoretical increase in detection to 94.2%. (35)

However, universal fetal echocardiography for pregnant women is unrealistic. Previous analyses that examined universal echocardiography suggested detection rates of, at most, 90% but, are probably realistically closer to 80%. (3)(4)(36) In the cost-effective analysis previously mentioned, the assumed 94.2% detection rate was probably overly optimistic. (35) If a detection rate closer to 80% is correct, the additional cost to the health-care system would have been even higher. (4)(35) In addition, the availability of adequately trained clinicians and sonographers may not be able to meet the increased demand. This deficit could potentially lead to a decrease in the quality of image acquisition and interpretation. (4) Such insufficiencies would either prevent patients from having the study or lead to substandard practice, neither of which are ideal scenarios. As such, universal screening with fetal echocardiography alone is not a viable option within our current health-care system.

FUTURE CONSIDERATIONS

Moving forward, there is a plethora of ways to potentially address the limitations of fetal anatomical cardiac screening and fetal echocardiography. Educational and training modalities remain paramount for clinicians to update their understanding of how to obtain and interpret imaging. (7) It is also important to ensure that these improvement efforts are bolstered and supported by access to seasoned and trained clinicians experienced in obtaining and reading cardiac views. (37) Lastly, the potential for quality assurance methods that involve review and constructive feedback of acquired images may potentially help identify clinicians and sonographers capable of appropriate image capture and interpretation. (37)(38)(39)

Education and training serves as a starting point and foundation for many clinicians and sonographers. Many articles and training modalities are available for clinicians to review and use. (7)(11)(12)(37) Many of these resources provide comprehensive, detailed guides that explain how to effectively obtain specific images. Applying these guides to actual patients is the next step in the process of practical application of such educational resources.

However, the ability of clinicians to effectively develop and refine these skills in isolation without appropriate oversight or guidance is not practical and potentially harmful. Referral to either MFM or pediatric cardiology specialists, as previously mentioned, is certainly appropriate to provide safe care. Ideally, referring clinicians who recommend fetal echocardiography should receive appropriate feedback and guidance about their image findings and presence of confirmed congenital heart defects. Unfortunately, this reality may not be possible in certain regions of the United States. The increasing use of telemedicine options for interpretation of these studies presents a possible avenue to make inroads to improve imaging acquisition. (40)(41)(42) Clinicians and sonographers in remote locations can transmit their images to centralized reading locations where trained MFM specialists and pediatric cardiologists can provide rapid and timely feedback. Logistically, the challenges of having clinicians available to interpret these images, as well as training sonographers to be independent enough to adequately capture and transmit their findings in a safe and secure manner, presents unique challenges that should not be taken lightly. (40)(41)

Some clinicians may also wonder whether referral to either MFM or pediatric cardiology specialists is the most appropriate next step in care. Some analyses suggest that when MFM and pediatric cardiology are able to collaborate with one another, the detection rates of cardiac anomalies are higher (84%). (43) In this model, MFM specialists review basic and comprehensive anatomy ultrasound scans and then refer cases suspicious for congenital heart defects to pediatric cardiology. (34)(43) Their ability to work together allows for cardiologists to provide their considerable expertise in fetal cardiac imaging and counseling while the MFM specialists gain experience and provide additional information to foster a more complete clinical understanding of the disease process.

All of this work is worthless unless there are effective approaches to determine if clinicians and sonographers are consistently and accurately obtaining cardiac images. At present, there are examples of methods to ensure standardized measurements of ultrasonographic findings such as nuchal translucency and growth parameters. (38)(39) In addition to developing effective tool kits and bundles to aid in the dissemination and education of clinicians, feedback from central organizations that can review and certify clinicians and sonographers as well as offer updates on approaches to image acquisition, would be especially helpful. (38) Whether this occurs with each iteration of recommended screening guidelines or continues longitudinally, such support would likely hasten skill development of clinicians and sonographers who are not well versed in cardiac imaging.

In conclusion, cardiac screening and fetal echocardiography are highly needed and desired tools to aid in the diagnosis of congenital heart defects. While research about the impact of fetal echocardiography on neonatal and childhood outcomes continues, there is already evidence to suggest that it is a cost-effective and appropriate tool to use in select patients at risk for congenital heart defects. Safeguarding against unnecessary referral and overutilization of care will require multifaceted and unique solutions to better ensure that patients receive appropriate studies from well-trained and supported sonographers and clinicians.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the importance and limitations of ultrasonographic findings of common fetal anomalies including congenital heart disease.

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1. Congenital heart defects are one of the most common fetal structural malformations, with an estimated prevalence in the United States of 8 in 1,000 live births. Which of the following statements regarding the fetal diagnosis of congenital heart defects is TRUE?

   A. The 4-chamber view alone is able to identify 75% of congenital heart defects.
   B. The addition of outflow tract views to the 4-chamber view enhances the detection rate of congenital heart defects to up to 90%.
   C. Confirmatory fetal echocardiography should not be performed until 20 to 22 weeks' gestation.
   D. By combining 4-chamber, outflow tract, and 3-vessel trachea views, the sensitivity of cardiac disease detection increases to 95%.
   E. A 4-chamber view at 18 to 22 weeks' gestation is the only view recommended by the American Institute of Ultrasound Medicine.

2. Up to 31% of infants with congenital heart defects have associated extracardiac malformations. Of these, anomalies are most frequently observed within:

   A. The renal system.
   B. The gastrointestinal system.
   C. The musculoskeletal system.
   D. The nervous system.
   E. The immune system.

3. A genetic cause is identified in about a third of infants with a congenital heart defect. Which of the following heart defects is most likely to be associated with an underlying genetic cause?

   A. Tetralogy of Fallot.
   B. Ventricular septal defect.
   C. Transposition of the great arteries.
   D. Total anomalous venous return.
   E. Coarctation of the aorta.

4. Referrals for fetal echocardiography have increased in recent years. These referrals are largely driven by suspected congenital heart defects on screening anatomical survey, increased nuchal translucency, and suboptimal imaging. Which of the following statements regarding referrals for fetal echocardiography is TRUE?

   A. The increase in maternal obesity is the most important cause of the increase in referrals for suboptimal imaging.
   B. The overall positive yield of fetal echocardiography is 30%.
   C. Suspected congenital heart disease by initial screening is most predictive of abnormal fetal echocardiography.
   D. The prenatal detection rate of congenital heart disease, by percentage of referrals, has increased over the past 10 years.
   E. Suboptimal imaging has a positive yield on fetal echocardiography of 20%, compared with almost 40% for suspected congenital heart disease by anatomical surveys.

5. From a health-care utilization perspective, the use of fetal echocardiography has been shown to be suboptimal. There is a goal to improve the cost-effectiveness for congenital heart disease screening while maximizing detection rates. Regarding this goal, which of the following statements is FALSE?

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2018 *NeoReviews* now is approved for a total of 10 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics through the ABP MOC Portfolio Program. Complete the first 5 issues or a total of 10 quizzes of journal CME credits, achieve a 60% passing score on each, and start claiming MOC credits as early as May 2018.

A. Screening by obstetrical clinicians followed by referral to maternal-fetal medicine (MFM) clinicians or pediatric cardiologists has been shown to be the most cost-effective strategy.
B. The availability of adequately trained clinicians and sonographers is a limiting factor in the implementation of cost-effective strategies.
C. The detection rate of a cardiac defect after referral to an MFM clinician is 50%.
D. More than 90% of cardiac defects would, in theory, be detected using a universal screening approach.
E. Universal screening with fetal echocardiography is the most cost-effective way to detect congenital heart diseases.

Understanding the Limitations of Fetal Cardiac Imaging

Patrick D. Schneider and Abraham Groner

NeoReviews 2018;19;e134
DOI: 10.1542/neo.19-3-e134

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Universal Screening for Perinatal Depression

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Education Gaps

1. Even those mothers who are well connected to the health-care system may not be recognized as having depression.
2. Validated screening tools to assess for maternal perinatal depression are needed.
3. Pediatricians and neonatologists may not feel adequately trained in addressing maternal depression.

Abstract

Perinatal depression, defined as maternal depression that occurs during the antenatal period or the first 12 months after delivery, is a leading cause of maternal morbidity. Although some women may have risk factors for the development of perinatal depression, screening based on risk factors alone is insufficient. In this article, we summarize the validated screening tools that have been used clinically to assess for perinatal depression. We then review the implementation process of universal screening during the obstetric and pediatric office visits and in the setting of the NICU. We conclude that obstetricians, neonatologists, and pediatricians can influence the quality of life for mothers and their children through successful implementation of validated screening tools for perinatal depression.

Objectives After completing this article, readers should be able to:

1. Describe the impact of perinatal depression on maternal and fetal well-being.
2. Describe screening instruments used to evaluate for perinatal depression.
3. Describe the implementation and importance of perinatal depression screening during the obstetric visit.
4. Describe the implementation and importance of perinatal depression screening during the pediatric visit.
5. Describe the implementation and importance of perinatal depression screening in the NICU.

AUTHOR DISCLOSURE Drs Diaz and Plunkett have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
ACOG	American Congress of Obstetricians and Gynecologists
CI	confidence interval
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EPDS	Edinburgh Postnatal Depression Scale
PHQ	Patient Health Questionnaire

INTRODUCTION

Depression is a primary cause of disability among women. (1) Perinatal depression specifically refers to depression that occurs during the antenatal period or the first 12 months after delivery. Depression accounts for a significant portion of mental health disorders diagnosed during pregnancy. One in 7 women experiences perinatal depression, making it the most common complication of pregnancy. (2) Maternal suicide contributes to maternal mortality more than hemorrhage and hypertensive disease. (3) Certain risk factors place a woman at increased risk of depression in the perinatal period. These risk factors include lack of social support, history of domestic violence, history of mood disorders, an unplanned pregnancy, or unanticipated complications during pregnancy. (4) However, reliance on these risks factors alone is insufficient to adequately identify all women who suffer from perinatal depression. (5)

Perinatal depression is associated with several antenatal morbidities. Both pregestational and gestational diabetes have been associated with depression during pregnancy. (6) Interestingly, depression in the antenatal period may also be associated with the subsequent development of preeclampsia. A prospective population-based study conducted in Helsinki, Finland, screened women at their initial prenatal visit for both depression and anxiety using a validated questionnaire. (4) A cohort of 652 women was subsequently followed throughout pregnancy to assess the risk of developing preeclampsia. Depression was associated with an increased risk for preeclampsia (odds ratio, 2.5; 95% confidence interval [CI], 1.2–5.3). (4) This association was found to hold true even after controlling for potential confounders such as smoking, profession, age, marital status, and the use of alcohol.

Depression during pregnancy has also been associated with an increased use of health-care resources during the antepartum and postpartum periods. A study from Northern Sweden evaluated a total of 1,495 women to assess differences in obstetrical outcomes and health-care consumption during pregnancy, delivery, and the early postpartum period. (7) Women diagnosed with depression during the second trimester of pregnancy were compared with healthy participants. The Primary Care Evaluation of Mental Disorders system was used to screen for depression, which has been validated for use in the primary care setting. Women with antenatal depression were found to suffer from nausea and vomiting more often and to use a significantly higher number of sick days compared with their healthy counterparts. Women with antenatal depression also tended to visit their obstetric providers more often and presented to labor and delivery for concerns of preterm contractions and fear of childbirth more frequently than their healthy counterparts. In addition, this cohort of women with antenatal depression had planned cesarean deliveries more often than their counterparts.

Perinatal depression also carries a significant risk to the child. A mother's postpartum depression can lead to poor mother-infant bonding and insecure attachment. (8) A recent meta-analysis demonstrated that untreated depression during the antenatal period is associated with increased neonatal distress after delivery, less than optimal neonatal orientation and motor activity, and disrupted sleep. Long-term effects on the child also have been reported, which include disruptive social behavior and pediatric depression. (9)

Thus, the detrimental effects of undiagnosed and untreated peripartum depression affect maternal morbidity and mortality, neonatal and childhood well-being, and health-care utilization. For these reasons, both the American Congress of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) recommend universal screening for women during the perinatal period. (2)(10) The objective of this review is to summarize the current screening tools available to assess for perinatal depression and review the approaches to implement a universal screening program in obstetric and pediatric offices and the NICU. For an overview of the specific outcomes of universal mood screening, refer to the review by Keesara and Kim in this issue of *NeoReviews*. (11)

VALIDATED SCREENING TOOLS

Edinburgh Postnatal Depression Scale

A number of screening tools are available to screen for depression in the perinatal period. However, the best method for detecting perinatal depression remains unclear. Given that certain symptoms such as fatigue, lack of energy, appetite, and sleep changes may be related to the pregnancy or peripartum period, it is important to use a screening tool that excludes these constitutional symptoms as markers of depression. One of the most commonly used and validated screening tools is the Edinburgh Postnatal Depression Scale (EPDS). (12) Both the ACOG and the AAP recommend using the EPDS scale to evaluate for perinatal depression. The EPDS consists of a series of 10 questions pertaining to a woman's feelings over the past 7 days. A score of greater than 12 or answering "yes" to the question relating to thoughts of self-harm suggest that a patient is at an increased risk for depression and further evaluation is warranted. Most women are able to complete the survey in less than 5 minutes. (2) Regardless of the score on the EPDS, any woman who expresses feelings of depression or anxiety should be sent to a qualified health-care practitioner for further evaluation, diagnosis, and possible treatment.

The EPDS was developed because instruments that screened for depression in the general population were found to be suboptimal when used for postpartum women. The use of the EPDS as a screening tool for postpartum depression was initially validated in 1987 on 84 mothers living in Edinburgh, Scotland; 72 women were thought to be at risk for depression and 12 women were not at risk. (13) In this study, a health-care practitioner, blinded to depression risk, conducted depression assessments during a home health visit. The EPDS was completed by the mother and the survey was then placed in a sealed envelope so that the interviewer remained blinded to the score while he/she conducted a standardized psychiatric interview. The 10-item EPDS was validated by comparing the EPDS scores with the standardized psychiatric interview results. The study demonstrated that women who had a score that was higher than 12 to 13 were more likely to have a depressive illness of varying severity. The EPDS in this particular cohort had a sensitivity and specificity of 85% and 77%, respectively. (13)

In 2001, 14 years after the introduction of the EPDS, a meta-analysis was published to review validation studies of the EPDS. (14) A systematic search was performed in Medline and the Science Citation Index to include studies published from 1987 to 2000. A total of 18 validation studies were identified. The size of the studies ranged from 53 to 147 participants. In some cases, there was overrepresentation of women with depression. In approximately half of the studies, the EPDS was validated against the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*, versions III, IIIR, or IV) criteria for depression. The remaining studies validated the EPDS against other standardized criteria including the Research Diagnostic Criteria, the Comprehensive Psychopathological Rating Scale–Depression, the Schedule of Affective Disorders and Schizophrenia, the Present State Examination, and the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)*. A broad range in both the sensitivity and specificity of the EPDS was noted between the studies (sensitivity of 65% to 100% and specificity of 49% to 100%). The cutoff scores of the EPDS scale ranged from 9.5 to 12.5. (14) As anticipated, studies with a high cutoff score for depression demonstrated a lower sensitivity and a higher specificity than studies with a low cutoff score. Similarly, the positive predictive value of the EPDS for detection of depression was higher in those studies in which depression was overrepresented. In these studies, the positive predictive value was found to be high, ranging from 44% to 76%. Using the rate of depression found in the general population of 13%, (15) the positive predictive value would be considerably lower. This finding points to the importance of clinical verification to make the diagnosis of depression after the EPDS screening tool is used.

Patient Health Questionnaire

The Patient Health Questionnaire (PHQ-9) screens for mood disorders. This tool denotes a score of “0” (not at all) to “3” (nearly every day) for each of the 9 *DSM-IV* criteria. It is unique because it is a self-administered diagnostic instrument designed for the primary care population. The “PHQ Primary Care Study” reported the validation and usefulness of the PHQ to diagnose mental health disorders in the primary care setting. (16) The study took place in 8 primary care clinics in the United States. A total of 3,000 adult patients were administered the PHQ by their primary care physician. PHQ diagnoses were compared with independent assessments from mental health professionals based on a phone interview. To be eligible for a phone interview, participants needed to be reached by phone within 48 hours of completing the PHQ. Of the 3,000 individuals, 585 had an interview with a mental health-care practitioner after completing the PHQ. A diagnosis based on the PHQ was made in 825 (28%) of the 3,000 participants and 170 (29%) of the 585 women who were interviewed. (16) There was good agreement between PHQ diagnoses and those of independent mental health practitioners (κ score, 0.65; overall accuracy, 85%; sensitivity, 75%; specificity, 90%). (15) This study met its objective of demonstrating the usefulness of the PHQ, and this screening instrument remains commonly used in the primary care setting.

Although administration of the PHQ has shown to be valid in the primary care setting, the inclusion of constitutional symptoms in this screening tool may reduce the sensitivity for detecting perinatal depression. A University of Pittsburgh study compared the EPDS with the PHQ-9. (17) Women older than 18 years who delivered an infant 6 to 8 weeks earlier were administered both the EPDS and the PHQ-9 via a telephone interview. A total of 135 women were reached. A home interview was subsequently conducted for those women who screened positive for an increased risk of depression. Of the 135 women reached, 123 (91%) were screened, of which 29 (24%) had home visits and 13 (11%) were diagnosed with major depressive disorder using the *DSM-IV* criteria. Using the standard cutoffs validated for each survey, the EPDS identified 8 patients (62%) with major depressive disorder, while the PHQ-9 validated 4 (31%). (17) This study emphasizes that while the PHQ-9 has been validated in the general population to screen for depression, it may not be the best test to use on patients during the perinatal period.

TWO-STEP APPROACH TO SCREENING

The US Agency for Healthcare Research and Quality suggests that serial testing be conducted to screen for perinatal depression to reduce false-positive results. (18)(19) This agency recommends that a sensitive, 2-question screening tool that assesses for feelings of depression or hopelessness and a lack of interest or pleasure in activities could serve as the initial screening tool. This screening tool would then be followed by a second, more specific instrument for women who respond affirmatively to either question. This sequential approach may be a reasonable strategy to reduce both false-positive and false-negative results. (19)

For example, the United Kingdom's National Institute for Health and Care Excellence routinely recommends asking all women in the postpartum period the following 2 questions (18)(20):

1. "During the past month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past month, have you often been bothered by little interest or pleasure in doing things?"

A meta-analysis was conducted to calculate the accuracy of these questions against the gold standard diagnosis of depression. The gold standard used was either the *DSM* or the *ICD*. A total of 10 studies met inclusion criteria. Asking these initial questions shows a consistently high pooled sensitivity (0.95; 95% CI, 0.88–0.99) and a modest pooled specificity (0.65; 95% CI, 0.56–0.74). (21)

IMPLEMENTATION OF UNIVERSAL PERINATAL DEPRESSION SCREENING

Although multiple barriers may exist with the identification, diagnosis, and treatment of perinatal depression, many providers and institutions have achieved success. The Department of Obstetrics and Gynecology at our institution, NorthShore University HealthSystem, devised a comprehensive and robust perinatal screening and treatment strategy that was successfully implemented (22) in 2003, and includes the following steps, which may serve as a blueprint for others:

1. Physician and nursing education on perinatal depression: A psychiatrist employed through the hospital provided a structured primer on perinatal mood disorders to the entire medical staff. This included information pertaining to research of the history of screening for perinatal depression and treatment options available to patients.
2. Development of a mental health provider network to provide sufficient referral options for women with depressive symptoms.
3. Establishment of a 24/7 depression hotline to respond to urgent mental health concerns.
4. Initiation of antenatal depression screening in addition to the 6-week postpartum screen.

The principal goal of this program was to identify perinatal depression as early as possible and respond with an assessment and intervention. Funding for the program was achieved through philanthropy, along with intramural and external grant support. Although provider participation in the program was voluntary, within the first year of the program all 20 obstetrical practices in the department participated. During the first 2 years, 4,558 perinatal depression screenings were performed and the perinatal depression hotline had received 514 calls, with 328 (64%) successful referrals to ongoing care. (22) The program today performs approximately 7,000 screenings annually and receives over 900 hotline calls with approximately 75% referrals to ongoing care (personal communication). The program remains in effect today and serves as a model of success for other health-care systems.

UNIVERSAL SCREENING IN PEDIATRIC PRACTICES

Although universal screening through obstetric practices successfully identifies women who present with peripartum depression, it misses a significant proportion. Most women conclude their obstetric care at their 6-week postpartum visit with their obstetric provider. Although the timing of the diagnosis of major depressive disorders peaks 6 weeks after delivery, many women have depressive symptoms after that time. Indeed, the peak in the diagnosis of minor depression occurs 2 to 3 months after delivery. (10) The risk of major depression continues during the ensuing 12 months after delivery and ranges from 1.0% to 6.8%. (5) Because mothers make frequent visits to the pediatrician's office during this 1-year period, the AAP Mental Health Task Force recommends integrating postpartum depression surveillance and screening at the 1-, 2-, 4-, and 6-month pediatric visits. (10)

Most pediatric practitioners agree that screening for perinatal depression is within the scope of their pediatric practice. In 2002, the AAP conducted a cross-sectional survey of primary care pediatricians to assess their self-reported responsibility, approach, and confidence in diagnosing and managing postpartum depression. This survey also asked pediatricians to identify barriers to recognition and management of postpartum depression and their willingness to be educated or to initiate new strategies to improve their approach. (23) A total of 888 pediatric providers were surveyed. In this study, 57% of pediatricians reported that it was their responsibility to recognize maternal depression. (23) Most physicians (58%) used cues such as the child's problems or mother's behavior, appearance, or complaints to identify maternal depression. (23) A minority (31%) were confident in their ability to diagnose postpartum depression. (23) If maternal depression was suspected, 29% of pediatricians referred the mother to a mental health-care provider, while 28% referred the patient to her primary care provider. (23) In addition to referral, 68% of pediatricians reported that they also provided brief interventions such as lifestyle modifications. (23) Understandably, most (95%) pediatricians did not feel comfortable with the treatment of postpartum depression in women. (23) Providers reported the most significant barriers to care were insufficient time to take a history and effectively counsel patients. Nonetheless, this study highlighted pediatricians' perceptions of their role in recognizing and effectively treating mothers suspected of having postpartum depression. Given that a portion of pediatricians remain uncomfortable with recognizing and treating depression, there remains room for improvement with respect to training pediatricians in this area. Residency programs and hospitals where pediatricians are employed may consider providing sufficient training and resources so that physicians feel competent and comfortable in diagnosing and treating mothers with depression.

The best screening approach in pediatric practices has not yet been determined. One study investigated the validity of a 2-question screen followed by administration of the PHQ-9 during health supervision visits. (24) The usefulness of this approach was compared with the reference standard for diagnosis of depression, the Structured Clinical Interview for the *DSM-IV*. A total of 506 participants were screened at 0 to 1, 2, 4, 6, and 9 months postpartum. The 2-question screen had a sensitivity of 100% for identifying postpartum depression and the 2-question screen with the PHQ-9 demonstrated a specificity of 80%. (24)

A subsequent study was performed in 2006 to evaluate an alternative approach for screening for postpartum depression. (25) Screening was done at 1 month and 6 months using the 2-question PHQ. This screening tool was chosen based on the US Preventive Services Task Force recommendation "that all adults receive depression screening with 2 questions that assess mood and anhedonia" (ie, inability to experience happiness with joyful activities) when visiting their health-care clinician. (25)

The following 2-question survey was used in the study:

1. "Over the past 2 weeks, you have felt down, depressed, or hopeless (true or false). If true, have you felt this way for (several days, more than half the days, or nearly every day)?
2. Over the past 2 weeks, you have felt little interest or pleasure in doing things (true or false). If true, have you felt this way for (several days, more than half the days, or nearly every day)?"(25)

Of note, no additional screening tool was used in this study. Instead, a positive screen prompted the pediatrician to discuss the impact of maternal depression on child health, offer self-help approaches, and refer to a mental health practitioner as needed. Importantly, all offices involved in the study had access to appropriate referral networks. In this study, a total of 1,398 women were screened in 3 rural pediatric practices. Of these, 238 mothers (17%) screened positive. (25) Clinical time constraints were modest, with 50% to 70% of pediatricians stating that they required no additional time, 20% to 30% required brief discussion (<3 minutes), and only 1% to 4% required 5 minutes or more. (25) This study serves as an example that if an appropriate screening tool and effective resources are embedded into a practice, screening for postpartum depression in the pediatrics office is feasible.

UNIVERSAL PERINATAL DEPRESSION SCREENING IN THE NICU

Perinatal depression screening may also be considered in the NICU. Recent studies suggest that mothers of preterm infants are at a higher risk of developing depression in the immediate postpartum period compared with mothers of term infants (15.4% vs 9.4%; $P<.001$). (15) This elevated risk continues throughout the first year after birth of a very low-birthweight infant compared with a normally grown infant (11.7% vs 9.7%, respectively, $P<.031$). (26) Another study conducted in the NICU setting for parents with newborns prenatally diagnosed with birth defects showed that 35.9% of mothers and 9.5% of fathers were at risk for depression. (27)

The Department of Pediatrics at the University of Oklahoma Health Sciences Center had a pilot program that screened mothers of infants admitted to the NICU. (28) Screening was done using the Postpartum Depression

Screening Scale, a 35-item self-reported Likert scale used to assess symptoms of postpartum depression. Screening began 14 days after delivery and was incorporated into routine screening procedures (eg, state newborn screening test). A nurse coordinator facilitated communication with mothers to discuss the purpose of the screening and to administer the questionnaire. Mothers who screened positive were referred to the psychology team for diagnostic interviewing. During the 18-month study period, 48% of eligible women completed the screen and 36% of these women had a positive screen that resulted in a mental health referral. (28) This study highlights the important role for implementation of perinatal depression screening in the NICU setting.

CONCLUSION

In summary, this review emphasizes the importance of recognizing and diagnosing perinatal depression. Untreated maternal depression can have significant adverse consequences for the mother as well as for the short- and long-term health of her child. Various screening tools have been validated for use in perinatal screening, such as EPDS, PHQ-9, and the 2-question PHQ. Each can be used to easily and effectively screen patients during the peripartum period. Screening in the obstetric office, NICU, and pediatric office may provide an optimal opportunity to identify women at risk for perinatal depression. Implementation of a screening program, however, is only as successful as the resources available for the treatment of mothers diagnosed with depression. Access to an appropriate referral network and adequate training of providers are key components to a successful program. Obstetricians, neonatologists, and pediatricians can influence the quality of life for mothers and their children through successful implementation of a screening and referral program for perinatal depression.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the effects on the fetus and/or newborn infant of maternal psychiatric disorders and their treatment.

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1. A mother who has just delivered her infant at term gestation is noted to have a history of domestic abuse. Due to this risk factor, a social worker is asked to assess the home environment and the mother's emotional health. Which of the following statements regarding depression during the perinatal period is correct?

   A. Although emotional lability is common during pregnancy and after childbirth, the incidence of clinical depression is relatively rare, at about 1 in 1,000 pregnancies.
   B. Risk factors for depression in the perinatal period include lack of social support, history of domestic violence, history of unplanned pregnancy, and unanticipated complications during pregnancy.
   C. In general, using a risk-factor approach to identify maternal depression has been shown to be an adequate and sufficient strategy to identify cases.
   D. Suicide during pregnancy is the third leading cause of maternal death, following hemorrhage and eclampsia/preeclampsia.
   E. The formal diagnosis of clinical depression in the perinatal period requires brain computed tomography or magnetic resonance imaging to rule out stroke or malignancy.

2. A 29-year-old woman during the second trimester of pregnancy is having sleep disruption, frequent bouts of anxiety and sadness, and difficulty with regular tasks. She is referred to a specialist and diagnosed with depression. Which of the following have been shown to be more likely in women who have depression during pregnancy?

   A. Preeclampsia.
   B. Planned vaginal delivery.
   C. Avoidance of the health-care system and decreased visits to obstetric providers.
   D. Neonatal tumors including Wilms tumor and retinoblastoma.
   E. Neonatal early-onset sepsis with *Listeria monocytogenes*.

3. You are discussing the use of screening tools for depression in the perinatal period with the clinic team. Your team is hoping to increase the awareness, identification, and referral of mothers who may have depression. Which of the following statements regarding available screening tools is correct?

   A. The Edinburgh Postnatal Depression Scale (EPDS) has been well validated, but is only applicable to women of European descent.
   B. Although the Patient Health Questionnaire is well validated, it has limited use due to the requirement that it should be administered by a trained psychiatrist.
   C. An advantage of the Patient Health Questionnaire is that it was specifically designed for the postpartum period.
   D. Both the American Congress of Obstetricians and Gynecologists and the American Academy of Pediatrics recommend the EPDS as a method to evaluate for depression during the perinatal period.
   E. Having a score on the EPDS of 10 or higher is a sufficient confirmatory diagnosis of depression.

4. A woman has had a routine pregnancy and delivery and is visiting the pediatrician's office for a 2-month health supervision visit. The mother is noted to have a flat affect and notes that she has had difficulty with feelings of hopelessness and inadequacy. Which of the following statements regarding screening for postpartum depression in pediatric offices is appropriate?

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A. Because mothers attend frequent visits to the pediatrician's office during the first 12 months after delivery, it may be beneficial to integrate postpartum depression surveillance and screening at the 1-, 2-, 4-, and 6-month pediatric visits.
B. Because pediatricians are not adequately trained in maternal depression, they should avoid attempts to perform diagnostic evaluations, including any sort of screening, in the official pediatric clinic setting.
C. Because postpartum depression peaks in the first 2 to 3 days after delivery, it is not feasible for clinic visits to serve as a useful setting for depression screening.
D. Most pediatricians do not feel that it is their responsibility to play a role in maternal depression.
E. Because the focus of the pediatric visit is on the infant, attempts to help the mother for depressive symptoms should occur at a separately scheduled appointment.

5. You are counseling a family, whose infant is in the NICU, regarding discharge planning. The infant was born at 28 weeks' gestational age and is now 6 weeks old, having made good progress clinically. As you speak to the mother, you note that she is aloof and seems uninterested. Staff members have previously noted that she seems depressed. Which of the following statements regarding perinatal depression in the NICU setting is correct?

A. It is natural for all mothers of preterm infants to feel a sense of loss, and efforts to acknowledge that loss will only make her feel worse.
B. The risk of maternal depression in the context of preterm delivery is 3 times as high as that for mothers of newborns prenatally diagnosed with birth defects.
C. Depression in mothers of preterm infants is rare in the immediate postpartum period because of the immediate shock of the circumstances and busy activities of the NICU, so efforts to address her symptoms should be postponed until the infant's discharge from the hospital.
D. Mothers of preterm infants are at higher risk of developing depression in the immediate postpartum period compared with mothers of term infants.
E. The most recent evidence points to postpartum depression in families of preterm infants affecting the father more than the mother, and occurring primarily when the infant is at home and of school age, not during the NICU course.

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Outcomes of Universal Perinatal Mood Screening in the Obstetric and Pediatric Setting

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Education Gaps

1. It is important to implement universal perinatal mood screening for parents of newborns.
2. Brief counseling sessions to address maternal mental health concerns must be conducted by trained midlevel clinicians.
3. A reliable referral linkage to mental health-care clinicians can improve health outcomes for women with symptoms of perinatal depression.

Abstract

Universal mood screening for pregnant women in the perinatal period has been recommended for both obstetric and pediatric settings. This review summarizes the body of evidence that supports universal mood screening in the perinatal period. Screening has been shown to increase detection of depression, especially in the inpatient setting. When implemented with immediate referral systems or brief counseling sessions, universal screening can increase rates of referral and treatment and lower rates of depression in the postpartum period. Immediate assessment systems can be used by midlevel health-care clinicians in the home visit, obstetric, and pediatric outpatient settings.

Objectives

After completing this article, readers should be able to:

1. Describe the effect of universal mood screening on rates of detection of maternal depression.
2. Describe the effect of universal mood screening on treatment of perinatal depression.
3. Describe the role of integration of brief counseling sessions with universal mood screening.
4. Describe outcomes for universal mood screening in the outpatient and inpatient pediatric settings.

AUTHOR DISCLOSURE Drs Keesara and Kim have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATION

EPDS	Edinburgh Postnatal Depression Scale

INTRODUCTION

Approximately 10% to 20% of women suffer from perinatal depression or anxiety. (1) During pregnancy and the postpartum period, women are at the highest risk in their lifetime of developing a mood disorder, getting admitted to a psychiatric facility, or completing suicide. (2) Antenatal depression has been associated with preterm delivery, low birthweight, and NICU admission. A mother's postpartum depression can lead to poor mother-infant bonding, insecure attachment, and possibly poor cognitive outcomes in her child. (3) The high frequency of health-care visits during a woman's pregnancy and in the child's first year provides an excellent opportunity to detect and treat maternal depression. (4) Both the American Congress of Obstetrics and Gynecology and the American Academy of Pediatrics recommend universal mood screening at least once during pregnancy or the postpartum period. (5)(6) This review serves to summarize data about outcomes of universal screening for perinatal mood disorders.

METHODS

We conducted a review of published literature catalogued in Ovid Medline, PyschINFO, Science Citation Index and Conference Proceedings (Web of Science), and PubMed from 1990 to 2017 using the following search terms: *postpartum, antenatal, perinatal, prenatal pregnancy, obstetric, postpartum period AND depression, mood disorder, affect, anxiety, anxiety disorder, depressive disorder*. Broadly, we searched for studies that reported outcomes from the use of validated perinatal mood screening questionnaires, favoring studies that compared groups of women who were screened to those who were not screened. Outcomes included prevalence, detection of depression, referral rates, treatment rates, and improvement in depressive symptoms. Studies that reported only implementation outcomes, such as the number of women screened and number of clinicians trained, were excluded. Experimental, quasiexperimental, and pre/post implementation studies were included. Cross-sectional studies that reported prevalence of perinatal depression as the only outcome setting were excluded if the study was conducted in the obstetric setting because prevalence data in these settings are well documented. However, pediatric studies that reported prevalence of maternal or paternal depression as the only outcome were included in this review because the literature in these settings is limited. Twenty-one studies met the criteria for inclusion; their design, results, and conclusions are summarized in the Table. In this article, we describe what this body of research suggests about the outcomes of universal perinatal depression screening and comment on implications for outpatient and inpatient pediatric care settings.

SUMMARY OF STUDY RESULTS

Universal Screening Increased Detection of Perinatal Depression

Universal screening for depression and anxiety with standardized questionnaires during pregnancy and the postpartum period detects more cases of women suffering from these disorders than does clinical judgment alone. Clinical judgment is limited by recognition of subtle signs of depression and patients' willingness to disclose symptoms. Patient's fear of stigma and negative experiences with clinicians who lack depression management skills can prevent admission of depressive symptoms. (7)(8) Evins et al compared universal screening to routine clinical detection in the outpatient setting, and found that universal screening increased detection of women at risk for postnatal depression in the year after delivery from 6.3% to 35.4%. (9) In a large retrospective study of almost 100,000 women in the outpatient setting, Avalos et al found detection of all depression increased from 8.2% to 11.5%, and detection of severe depression increased from 0.2% to 6.5% after implementation of universal screening. (10) Routine screening in the inpatient setting may be just as important, because patients may be at risk of developing depression while admitted. Byatt et al showed that 27% of women admitted for high-risk obstetrical issues were at risk for postnatal depression. (11)

Some argue that screening only women with risk factors for depression, such as history of mental health illness or intimate partner violence, would be most cost-effective and efficient. However, Berger et al compared universal screening to high risk factor screening, and found that risk-based screening missed 36% of the women in the study who screened positive for depression. Furthermore, Berger et al found that only 29 women needed to be screened to detect 1 woman at risk for depression. (12)

Screening Without Further Assessment Lacks Benefit

Screening is not clinically useful if the detected cases of women at risk for depression are left untreated. A number of studies have shown that screening without immediate assessment or linked referral does not lower rates of depression or increase treatment for depression. In a prospective observational study, Rowan et al screened 2,199 women for depression, and found that none of the 102 participants with elevated antepartum Edinburgh Postnatal Depression Scale (EPDS) scores sought mental health services during pregnancy.

TABLE. Studies Reporting Outcomes from Universal Mood Screening Interventions

REFERENCE	STUDY DESIGN (N)	SETTING	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Gerrard et al (16)	Retrospective cohort (N = 2,009)	Maternal and child health home visit	Pre and post training of home health visitors to recognize and counsel for postpartum depression	6 month postpartum EPDS scores >12	Decrease in high EPDS scores (>12) at 6 months: 19.3% vs 9.8%	Interventions that integrate screening and immediate counseling decrease number of women at risk for postpartum depression
Evins et al (9)	Randomized controlled trial (N= 79)	Obstetric clinic	EPDS screening compared to routine clinical evaluation in first year after delivery	Detection of rate of depression	Detection of women at risk for depression: 6.3% vs 35.4%	Universal screening of perinatal depression increases detection of postpartum depression
MacArthur et al (17)	Clustered randomized controlled trial (N = 2,064)	Maternal and child health home visit	Care from midwives trained to screen for postpartum depression and counseling compared to usual care	Depression scores at 4 months postpartum	Reduced EPDS score at 4 months postpartum in intervention group; improved perception of quality of care	Brief education along with screening can prevent and decrease rates of depression
Chaudron et al (26)	Retrospective cohort study (N= 220)	Pediatric clinic	Pre and post implementation of universal screening during health supervision visits	Detection of depression, referral to mental health care	Detection of depression: 1.6% vs 8.5%; referral for mental health care: 0.2% vs 3.6%	Universal screening of perinatal depression in pediatric setting can increase diagnosis of maternal depression and increase referral to mental health care services
Wickberg et al (20)	Randomized controlled trial (N= 669)	Maternal and child health home visit	Care received by midwives trained to screen for and recognize depressive symptoms compared to usual care	EPDS score >11 at 25 weeks compared to 36 weeks	Statistically significant greater drop in percentage of women who scored >11: 15.1% to 9.5% vs 12.8% to 11.6%	Brief education along with screening can prevent and decrease rates of depression during the antenatal period
Yonkers et al (14)	Observational cohort study (N= 1,336)	Obstetric clinic	Groups enrolled and not enrolled in New Haven Health Start Initiative depression screening and recommendation to seek treatment	Rate of detection, referral, and treatment	Similar detection in rate of depression: 6% vs 5%; similar referral and treatment: 1% vs 1%	Screening without brief intervention or referral does not decrease depression rates or increase rates of treatment for depression

Continued

TABLE. **(Continued)**

REFERENCE	STUDY DESIGN (N)	SETTING	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Morrell et al (18)	Clustered randomized controlled trial (N= 4,084)	Family practice clinic	Health visitors trained to identify depressive symptoms with EPDS and provide brief counseling at 6 weeks postpartum care	EPDS scores >12 at 6 months after delivery	Reduced percentage of women with scores >12: 34% vs 46%; 9 women needed to screen and counsel to reduce risk of depression for 1 woman	Brief education along with screening can prevent and decrease rates of depression
Leung et al (15)	Randomized controlled trial (N= 462)	Maternal and child health clinic	EPDS with nondirective counseling compared to clinical judgment	Detection of depression and rate of treatment	At 2 months postpartum increased detection of depression: 6.0% vs 29%; increased treatment: 4.8% vs 23.8%; 25 women needed to screen to detect 1 case of depression	Universal and systematic screening shows improved detection and treatment
Glavin et al (19)	Prospective cohort study (N= 2,247)	Maternal and child home visit	Screening at 6 weeks, 3 months, 6 months, 12 months with supportive counseling	Rates of screening and rates of depression	Higher rates of screening: 73% vs 95%; lower rates of depression at all time points	Brief education along with screening can prevent and decrease rates of depression
Feigelman et al (23)	Randomized controlled trial (N= 558)	Pediatric clinic	Training assessment of psychosocial issues for pediatric residents	Parent satisfaction	Increased parent satisfaction with child wellness services on a 5-point Likert scale	Screening for depression can improve patient satisfaction with child wellness services
Yawn et al (21)	Randomized controlled trial (N= 1,897)	Family practice clinic	Screening in primary care setting and tools to facilitate diagnosis, follow-up, and management of postpartum depression	Detection, treatment of postpartum depression	Increased diagnosis of depression: 41% vs 66%; higher rates of treatment of depression with medication and counseling: 37% vs 60%	Brief education along with screening can prevent and decrease rates of depression during the postpartum period
Rowan et al (13)	Prospective observational study (N= 2,199)	Multispecialty clinic	Screening with EPDS, recommendation for treatment, and phone call for those scoring >14	Patients who sought medical care	102 women scored >14 on EPDS, none sought mental health care; 569/2,199 were screened at 6 weeks; 5/28 who scored >14 EPDS sought referral	Screening without immediate linkage to referral does not lead to treatment for depression
Miller et al (22)	Retrospective cohort study (N = 541)	Maternal and child clinic	Perinatal Depression Management Program in urban clinic setting that trained providers in screening, treatment engagement strategies and immediate referral	Screening, assessment and treatment	Preimplementation: 65.2% completed screening with just 10% receiving on-site assessment, and none entering treatment; postimplementation: 93.5% completed screening, 84.8% received on-site assessment, and 90% diagnosed with depression entered treatment	Incorporating immediate assessment and referral with screening improves detection and treatment

Continued

TABLE. **(Continued)**

REFERENCE	STUDY DESIGN (N)	SETTING	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Byatt et al (11)	Cross-sectional observational study of inpatients (N= 82)	Obstetric inpatient		Prevalence of depression	EPDS >10: 27%; mental health treatment: 5%	Universal screening of inpatients shows increased rate of perinatal depression than in general population
Carroll et al (25)	Randomized controlled trial (N= 3,250)	Pediatric clinic	Automated perinatal screening reminders vs standard of care	Detection of depression, referral to mental health services	Detection of depression (1.2% vs 8.7%; OR 7.9) and anhedonia (0.4% vs 5.2%; OR 12.58); increased referral for mental health services: 1.2% vs 2.4%	Automated universal perinatal depression screening in pediatric setting increases detection of screening and referral to mental health services
Emerson et al (28)	Prospective observational study (N= 200)	Pediatric emergency department	Screening of mothers bringing their children to the emergency department	Prevalence of women at risk for depression who present to the pediatric emergency department	16% (31/200) women with EPDS >10	Universal screening can be used in a pediatric emergency department to identify missed cases of perinatal depression
Kingston et al (24)	Cross-sectional survey patients perception of benefits and harms of screening (N= 238)	Obstetric clinic		Perceptions of perinatal mood screening	78% reported feeling that provider cared; 68% were glad to be asked; 17% reported at least 1 harm including embarrassment or unknown goal of questions	Universal mood screening is a positive experience for most women and conveys a sense of caring from the health-care provider
Berger et al (12)	Retrospective cohort study (N = 537)	Obstetric clinic	Universal screening of perinatal mental health compared to screening just women with history of mental health disorder	Rate of detection	Universal screening yields 3.4% positive screening, with an NNT of 29, while women with risk factors for mental health yield a 15.3% positive screen with an NNT of 6; screening only high-risk women may miss up to 36% of positive screens	Universal screening of perinatal depression has NNT of 29 to yield a positive screen
Trost et al (29)	Prospective cohort study (N= 310)	Pediatric inpatient	Screening of all parents of hospitalized infants	Prevalence of women at risk for postpartum depression within 1 year of delivery	28% of mothers with elevated EPDS score	Inpatient pediatric settings may detect higher levels of postpartum depression

Continued

TABLE. **(Continued)**

REFERENCE	STUDY DESIGN (N)	SETTING	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Avalos et al (10)	Retrospective cohort study (N= 97,678)	Obstetric clinic	Preimplementation vs roll-out vs fully implemented universal screening in antenatal and postpartum visits	Detection of depression, treatment of depression	Detection of depression: 8.2% vs 11.5% treated of expected; depressed: 42.6% vs 47.1% treated of expected; severely depressed: 5.9% to 81.9%; ≥50% improvement in symptoms: 60.2% vs 59.4	Universal screening protocol with integrated referral compared to clinical judgment leads to increased diagnosis of depression, increased treatment, and reduced depression at 6 months
Cole et al (30)	Observational cohort (N = 1,327)	Pediatric inpatient	Administration of postnatal depression screening to parents with children with prenatally diagnosed birth defects	Prevalence of parents at risk for depression	Elevated risk for depression in the immediate postpartum period: 35.9% of women and 9.5% of men	Parents with infants in the NICU may have a higher risk of postpartum depression

EPDS=Edinburgh Postnatal Depression Scale; NNT=number needed to treat; OR=odds ratio.

Twenty-eight of 579 participants in that study who were screened 6 weeks after delivery had elevated EPDS scores, and only 5 sought mental health care. (13) Yonkers et al found no increase in detection, referral, or treatment for women enrolled in New Haven Health Start, a program that implemented universal screening with a recommendation for further assessment, but without immediate assessment or referral. (14)

Screening Combined With Assessment and Referral Linkages Improves Outcomes

When mood screening is integrated with immediate assessment or brief counseling sessions, there is an increase in the rate of detection and initiation of treatment, and a decrease in perinatal depression scores. In the randomized controlled trial by Leung et al, screening with immediate counseling was compared with clinical judgment and referral, and levels of detection and treatment increased at 2 months and rates of probable depression at 6 months decreased. (15)

Interventions that use home visits to screen, assess, and briefly counsel show a powerful impact on reduction of perinatal depression. Gerrard et al found that 10% fewer patients presented with high EPDS scores at their 6-month postpartum visit when they received care from a midwife who was trained to screen and counsel patients during home postpartum visits. (16) The training provided for the midwives was brief and occurred in a workshop setting during 10 sessions. (15) Three newer studies in the United Kingdom with similar interventions showed that training home health-care clinicians to recognize perinatal mood disorders and screen and provide brief counseling during postpartum visits led to a reduction in rates of depression at 6 weeks postpartum and reduced EPDS scores at 4, 6, and 12 months postpartum. (17)(18)(19) Wickberg et al observed a drop in depression scores from the 25th week of gestation to the 36th week of gestation when midwives were trained to screen and provide counseling during antenatal visits. (20)

Integration of screening and assessment in an outpatient clinic setting also increases detection, referral to mental health care, and treatment of depression with medication. A randomized trial by Yawn et al in a US family practice setting showed that training health-care workers in recognition and referral strategies for managing depression increased the diagnosis of depression and treatment with medication and counseling. (21) In an urban clinic setting, Miller et al showed that implementing universal screening and an immediate referral system increased onsite assessment from 10% to 84.8% and referral for treatment from 0% to 90% for women who were diagnosed with depression. (22) After implementation of a standardized perinatal screening and referral process in a large hospital system, Avalos et al showed that treatment of mild depression rose modestly from 42.6% to 47.1%, but treatment of severe depression increased from 5.9% to 81.9%. (10)

Universal Screening Increases Patient Satisfaction

Patient satisfaction improves when screening for depression is incorporated into outpatient visits. An intervention that trained pediatric residents in psychosocial assessment of children's families, including perinatal depression, showed that parents who participated in the intervention were more satisfied with their care. (23) A qualitative study of pregnant women who were screened for depression during their prenatal care expressed that mood screening made them feel their physicians cared more about them. (24) In a study that incorporated screening into home visits, patients who received screening were more likely than patients who received usual care to report "better than expected" care provided. (16)

Universal Mood Screening for Parents in Pediatric Settings Increases Detection

Universal screening for maternal depression during pediatric health supervision visits in the first year of an infant's life can improve detection of the development of perinatal depression that was missed or that developed after the initial postpartum visit. Carroll et al showed that compared with clinical judgment, automated reminders for maternal mood screening increased the detection of depression from 1.2% to 8.7% and increased referral to mental health services from 1.2% to 2.4%. (25) The evaluation by Chaudron et al of universal screening in a pediatric outpatient setting showed an increase in detection of depression from 1.6% to 8.5%. Referral to social work for mental health care increased from 0.2% to 3.6%. (26)

Parents whose children require additional medical care or department visits may be at increased risk for depression. Postpartum depression has been associated with increased health-care utilization in the pediatric setting. (27) One study that evaluated implementation of universal depression screening in the pediatric emergency department in 200 parents showed a 16% prevalence of perinatal depression. (28) Another cross-sectional study conducted with parents of inpatient infants showed a rate of 28% with an elevated EPDS score. (29) Another study conducted in the NICU setting of parents with newborns prenatally diagnosed with birth defects showed that 35.9% of mothers and 9.5% of fathers were at risk for depression. (30) While screening in these settings may be feasible and show higher rates of perinatal depression, as noted in these studies, this information may not be clinically useful unless immediate assessment and referral mechanisms are put in place.

DISCUSSION

The growing body of evidence shows that universal screening for perinatal mood disorders can increase detection of cases, promote treatment of depression, and improve patient satisfaction with care. While clinical judgment alone may detect severe cases of maternal depression, universal screening can detect more subtle mood disorders. With specific questions about mood in the screening questionnaires, clinicians may be better able to identify symptoms of depression. Importantly, mothers may be more willing to disclose symptoms of depression under these circumstances. Increasing the detection of depressive symptoms in the perinatal time frame creates an opportunity to treat depression in its early stages.

Screening, in conjunction with protocols for follow-up assessment and referral linkage, increases treatment of women with depression and reduces depressive symptoms. Immediate follow-up assessment after a positive screen for depression is especially important. These assessments can be performed by midlevel clinicians who are trained to recognize depressive symptoms, and perform brief counseling sessions for women at risk for depression. As evidenced by studies performed in the United Kingdom, training midlevel clinicians with these skills can be completed in a short workshop format over a few sessions.

Universal screening and follow-up in outpatient and inpatient pediatric care settings can increase detection and improve treatment for mothers with depression. Although there are no studies that report pediatric outcomes, in theory, improvement in maternal mood can improve attachment, parent-child relationship, and maternal functioning in the caregiver role. The outpatient pediatric setting is a critical access point to screen for the development of postpartum depression over the first year because mothers are likely to see their child's pediatrician multiple times during this year. Screening in inpatient pediatric settings, including NICU settings, can identify mothers who are more at risk for depression due to health complications of their child.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the effects on the fetus and/or newborn infant of maternal psychiatric disorders and their treatment.

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Selective Serotonin Reuptake Inhibitor Use in Pregnancy: Repercussions on the Oblivious Passenger

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Education Gaps

1. It is important to understand the safety profile of selective serotonin reuptake inhibitors with regard to teratogenicity.
2. It is important to understand the safety profile of selective serotonin reuptake inhibitors in the perinatal period.

Abstract

Depression is one of the most common comorbidities in pregnancy, and use of selective serotonin reuptake inhibitors (SSRIs) has become increasingly more common during this period. For this reason it is essential to understand the implications of SSRI use on fetal development and neonatal complications. As reviewed here, the preponderance of evidence suggests that the risk of teratogenicity with SSRI use is low. Poor neonatal adaptation or withdrawal syndrome is common among neonates exposed to SSRIs in the third trimester of pregnancy. However, the risk of severe neonatal adaptation syndrome, which would require neonatal intensive care, is low. The association between SSRI exposure and persistent pulmonary hypertension of the newborn remains controversial, but the evidence suggests a weak relationship with this rare outcome. The decision to initiate an SSRI in pregnancy should be individualized. Providers caring for pregnant women using SSRIs should feel comfortable discussing possible neonatal adaptation syndrome associated with the antenatal use of SSRIs, with a primary focus on appropriate treatment of maternal depression after discussion of risks and benefits.

Objectives After completing this article, readers should be able to:

1. Describe the influence of selective serotonin reuptake inhibitor (SSRI) use during pregnancy and its association with birth defects.

AUTHOR DISCLOSURE Drs Rodriguez-Kovacs, Tien, and Plunkett have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

aOR	adjusted odds ratio
CI	confidence interval
FDA	Food and Drug Administration
OR	odds ratio
PPHN	persistent pulmonary hypertension of the newborn
RR	relative risk
SSRI	selective serotonin reuptake inhibitor

2. Describe the association between perinatal use of SSRIs and neonatal adaptation syndrome.
3. Describe the association between SSRI use in pregnancy and persistent pulmonary hypertension of the newborn.
4. Describe the effects of SSRI use on breastfeeding.

INTRODUCTION

Recent evidence suggests that approximately 10% to 15% of women will experience major depressive disorder in the perinatal period, which is at least as common as rates reported for women in nonreproductive states. (1)(2) Use of antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs), also called *serotonin reuptake inhibitors*, has increased significantly among pregnant women in recent decades. (3) These agents, which traverse the placenta, have been inconsistently implicated in congenital anomalies in children whose mothers were exposed to SSRIs during the first trimester. In addition, SSRI use during and throughout pregnancy may have additional implications for neonatal outcomes. This review aims to explore the current evidence for SSRI use in pregnancy with a focus on teratogenicity, neonatal adaptation syndrome, persistent pulmonary hypertension of the newborn (PPHN), and breastfeeding.

CONGENITAL ANOMALIES AND SSRIs

A considerable amount of literature has been published on SSRIs and birth defects with conflicting findings. The results of these studies can best be categorized under 2 headings: studies that demonstrate teratogenicity related to SSRI exposure or potential exposure (Table 1), and studies that demonstrate no evidence of teratogenicity related to SSRI exposure or potential exposure (Table 2).

STUDIES DEMONSTRATING TERATOGENIC EFFECT

Studies demonstrating teratogenicity are primarily retrospective and case control in nature, with their inherent limitations. A register-based retrospective cohort study from Denmark (N=1,051) found that for any SSRI prescription filled from 30 days before conception until the end of the first trimester, there was a higher risk for cardiovascular malformations (odds ratio [OR], 1.4; 95% confidence interval [CI], 1.1–1.8). (4) Another study in 2012 from the same database found that offspring of women filling a prescription for an SSRI during the first trimester of pregnancy (N=4,183) had an increase in major anomalies (OR, 1.33; 95% CI, 1.16–1.53) and congenital heart defects (OR, 2.01; 95% CI, 1.60–2.53). (5) They also found an association between exposure to SSRIs in the first trimester and craniosynostosis, with an adjusted OR of 1.94 (95% CI, 1.00–3.76). A cohort study based on Danish administrative register data linked with the Danish EUROCAT that included 72,290 patients demonstrated an increased risk for severe congenital heart disease in children of women who used SSRIs in the first trimester (adjusted OR [aOR], 4.03; 95% CI, 1.75–9.26). (6)

A Nordic register-based case-control study included a sibling controlled design with 36,772 liveborn infants with presumed first-trimester exposure to any SSRI. (7) Risk estimates were increased for all major malformations combined (aOR, 1.13; 95% CI, 1.06–1.20), any cardiac defect (aOR, 1.15; 95% CI, 1.05–1.26), clubfoot (aOR, 1.34; 95% CI, 1.05–1.71), and omphalocele (aOR, 2.11; 95% CI, 1.01–4.39). However, the sibling controlled analysis that only included sibling pairs discordant for the exposure to SSRIs showed no increased risk for any of the aforementioned malformations; this suggests that the small increased risk found initially could be explained by unadjusted factors. (7)

The EUROCAT database compared SSRI exposure among cases with congenital heart defects or other malformations and controls. (8) The study failed to confirm prior associations with anencephaly, craniosynostosis, or limb reduction defects for presumed exposure to any SSRI. The study confirmed previously reported increased risk estimates for clubfoot (aOR, 2.41; 95% CI, 1.59–3.65) and renal dysplasia (aOR, 3.01; 95% CI, 1.61–5.61). The study also found heightened risk estimates for congenital heart defects combined (aOR, 1.41; 95% CI, 1.07–1.86), as well as increased risks specifically for tetralogy of Fallot (aOR, 3.16; 95% CI, 1.52–6.58) and Ebstein anomaly (aOR, 8.23; 95% CI, 2.92–23.16), neither of which had been previously reported in association with SSRIs. In addition, the risk estimates were increased for anorectal atresia and stenosis (aOR, 2.46; 95% CI, 1.06–5.68) and gastroschisis (aOR, 2.42; 95% CI, 1.10–5.29), respectively. A meta-analysis in 2013 that included 27 studies reported an association with

TABLE 1. **Evidence to Support an Association Between First-Trimester SSRI Exposure in Pregnancy and Congenital Anomalies**

REFERENCE	STUDY DESIGN (N)	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Wogelius et al (4)	Retrospective population-based cohort (N=151,831)	Exposure to SSRIs in any trimester	Congenital malformations	Congenital malformations associated with SSRI use in early pregnancy—aRR 1.34 (95% CI 1.00–1.79) and during the second or third month after conception—aRR 1.84 (95% CI 1.25–1.71)	Increased risk of congenital malformations after exposure to SSRIs in early pregnancy
Malm et al (9)	Retrospective population-based cohort (N=635,583)	Exposure to SSRIs during the first trimester	Congenital anomalies	Fluoxetine-associated isolated VSDs—aOR 2.03 (95% CI 1.28–3.21) Paroxetine RVOT defects—aOR 4.68 (95% CI 1.48–14.74) Citalopram NTD—aOR 2.46 (95% CI 1.20–5.07)	Fluoxetine use is associated with an increased risk of isolated VSDs Paroxetine is associated with RVOT defects Citalopram is associated with NTDs
Jimenez-Solem et al (5)	Register-based retrospective cohort (N=848,786)	Exposure to SSRIs during the first trimester vs women who paused exposure during pregnancy vs unexposed women	Major congenital malformations	CHD similar for exposed during first trimester—aOR 2.01 (95% CI 1.60–2.53) compared with paused treatment during pregnancy—aOR 1.85 (95% CI 1.07–3.20), *P*=.94	Increased risk of CHD if exposed to SSRIs throughout the first trimester, similar for women who used an SSRI but discontinued it during pregnancy
Munch et al (10)	Register-based retrospective cohort (N=1,928,666)	Maternal characteristics, maternal medical diseases, and medicine intake during pregnancy	Congenital hydrocephalus	Increased risk of isolated congenital hydrocephalus after maternal use of SSRIs—RR 2.7 (95% CI 1.5–4.6)	Significantly increased risk of isolated congenital hydrocephalus
Knudsen et al (6)	Register-based retrospective cohort (N=72,280)	Prescriptions for SSRIs filled during pregnancy	CHD	SSRI use during first trimester increased the risk of severe CHD—aOR 4.03 (95% CI 1.75–9.26)	Maternal use of SSRIs during first trimester increases the risk of severe CHD; no increased risk of septal defects was detected
Knickmeyer et al (11)	Retrospective cohort (N=189)	Prenatal SSRI exposure	Chiari I malformation on MRI scans at 1 and/or 2 years of age	Chiari I malformation—OR 10.32 (95% CI 2.04–102.46)	Marked increase of Chiari I malformation in children of depressed mothers treated with SSRIs during pregnancy
Ban et al (12)	Population-based cohort (N=349,127)	First-trimester SSRI or tricyclic antidepressants	Major congenital anomalies	Major congenital anomalies were not associated with SSRIs—aOR 1.01 (95% CI 0.88–1.17), or TCAs—aOR 1.09 (95% CI 0.87–1.38)	Major congenital anomalies risk did not increase with maternal depression or with antidepressant prescriptions

Continued

TABLE 1. **(Continued)**

REFERENCE	STUDY DESIGN (N)	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Yazdy et al (13)	Population-based case control (N=2,624)	SSRI use for a greater than 30-day period in lunar months 2 and 3	Clubfoot	Clubfoot and SSRI—OR 1.8 (95% CI 1.1–2.8)	Increased risk of clubfoot occurrence in relation to SSRI use
Furu et al (7)	Population-based case control (N=2,303,647)	Use of SSRIs or venlafaxine in early pregnancy	Birth defects, with emphasis on cardiovascular birth defects	All major malformations combined—aOR 1.06 (95% CI 0.91–1.24) CHD—aOR 0.92 (95% CI 0.72–1.17) Right ventricular outflow tract obstruction—aOR 1.48 (95% CI 1.15–1.89) ASD and VSD—aOR 1.17 (95% CI 1.05–1.31)	Septal defects and RVOT defects were higher in exposed infants
Wemakor et al (8)	Population-based case control (N=2,177,9770	First-trimester exposure to SSRIs	Specific CHD and other congenital anomalies	CHD—aOR 1.41 (95% CI 1.07–1.86) Severe CHD combined—aOR 1.56 (95% CI 1.02–2.39) Atrial septal defect—aOR 1.71 (95% CI 1.09–2.68) Tetralogy of Fallot—aOR 3.16 (95% CI 1.52–6.58) Ebstein anomaly—aOR 8.23 (95% CI 2.92–23.16) Anorectal atresia and stenosis—aOR 2.46 (95% CI 1.06–5.68) Gastroschisis—aOR 2.42 (95% CI 1.10–5.29)	Congenital anomalies associated with SSRI use include severe CHD, anorectal atresia, and gastroschisis
Bérard et al (14)	Retrospective cohort (N=18,487)	First-trimester exposure to antidepressants	Major congenital malformations	Major congenital malformations overall—aOR 1.07 (95% CI 0.93–1.22)	There was no association of major congenital malformations overall and SSRI use
				Paroxetine CHD—aOR 1.45 (95% CI 1.12–1.88) and ASD/VSD—aOR 1.39 (95% CI 1.00–1.93)	Certain SSRI use in first trimester increases the risk of cardiac and musculoskeletal malformations, as well as craniosynostosis
				Citalopram musculoskeletal defects—aOR 1.92 (95% CI 1.40–2.62) and craniosynostosis—aOR 3.95 (95% CI 2.08–7.52)	

aOR=adjusted odds ratio; aRR=adjusted relative risk; ASD=atrioventricular septal defect; CHD=congenital heart disease; CI=confidence interval; NTD=neural tube defect; RVOT=right ventricular outflow tract; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; VSD=ventricular septal defect.

TABLE 2. Evidence that Suggests No Association Between First-Trimester SSRI Exposure in Pregnancy and Congenital Anomalies

REFERENCE	STUDY DESIGN (N)	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Kulin et al (15)	Prospective multicenter cohort (N=267)	Exposure to fluvoxamine, paroxetine, or sertraline during the first trimester	Major congenital malformations	Congenital malformations—RR 1.06 (95% CI 0.43–2.62)	Fluvoxamine, paroxetine, or sertraline do not increase the risk of congenital malformations
Malm et al (16)	Population-based cohort (N=1,782)	SSRI purchase in any trimester	Major malformations, preterm birth, small for gestational age, low birthweight, and treatment in NICU	Major malformations purchase 4.2% vs no purchase 3.5% (*P*=.6) Treated in neonatal special or intensive care unit, third trimester purchase 15.7% vs first trimester 11.2% (*P*=.009)—aOR 1.6 (95% CI 1.1–2.2)	Use of SSRIs during pregnancy is not associated with increased risk of adverse perinatal outcome other than need for treatment in the neonatal special or intensive care unit
Wen et al (17)	Retrospective cohort (N=972)	SSRI prescription in the year before delivery	Adverse pregnancy outcomes	Major structural anomalies, exposed 2.1% vs not exposed 2.0%—aOR 0.98 (95% CI 0.59–1.64) Minor structural anomalies exposed 3.6% vs not exposed 3.4%—aOR 1.02 (95% CI 0.69–1.51)	SSRI exposure 1 year before delivery showed no increase in the risk of birth defects
Reis and Källén (18)	Retrospective cohort (N=14,821)	Reported use or prescription of antidepressants in early pregnancy	Congenital malformations	Relatively severe malformation—OR 1.08 (95% CI 0.97–1.21) Ventricular or atrial septal defect—OR 1.00 (95% CI 0.77–1.29)	No indication of a teratogenic effect
				Paroxetine—OR 1.66 (95% CI 1.09–2.53)	Association between paroxetine use and CHD
Nordeng et al (19)	Prospective cohort (N=63,395)	First-trimester exposure to SSRIs	Congenital malformations	Congenital malformations—aOR 1.22 (95% CI 0.81-1.84) Risk of CHD—aOR 1.51 (95% CI 0.67-3.43)	Exposure to SSRIs during the first trimester was not associated with increased risk for congenital malformations or CHD
Margulis et al (20)	Retrospective cohort (N=149,464)	First-trimester SSRI use	CHD	CHD—OR 1.00 (95% CI 0.50-2.00) Septal defects—OR 1.15 (95% CI 0.46-2.87)	No association between maternal use of SSRIs in early pregnancy and CHD or septal defects in the offspring
Reis and Källén (21)	Retrospective cohort (N=10,511)	Maternal use of SSRIs, sedatives, or the combination of both	Congenital malformations and CHD	Congenital malformations—OR 1.17 (95% CI 0.70-1.93) CHD—OR 1 1.14 (95% CI 0.37-2.67)	No evidence of a synergistic teratogenic effect of the combination of SSRIs and benzodiazepines

Continued

TABLE 2. **(Continued)**

REFERENCE	STUDY DESIGN (N)	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Huybrechts et al (22)	Prescription-based retrospective (N=949,504)	Antidepressant use during the first trimester	Major cardiac defects	Cardiac defect—aRR 1.06 (95% CI 0.93-1.22)	No increased risk of CHD
Ban et al (12)	Population-based cohort (N=349,127)	First-trimester SSRI or tricyclic antidepressants	Major congenital anomalies	aOR 1.01 (95% CI 0.88–1.17)	Major congenital anomaly risk did not increase with antidepressant prescriptions
Norby et al (23)	Register-based prospective cohort (N=741,040)	Exposure to antidepressants in utero	Rate of admissions to NICU, infants' morbidity and neonatal interventions	Birth defects—OR 1.00 (95% CI 0.9–1.2) CHD—OR 1.00 (95% CI 0.9–1.2)	No increase in risk of birth defects or CHD
Petersen et al (24)	Prescription-based retrospective (N=209,135)	Different antidepressant exposures before and during pregnancy	Congenital heart anomalies up to 5 years of age	CHD—OR 1.00 (95% CI 0.65–1.52) Independent of antidepressant prescribing: Diabetes—OR 2.23 (95% CI 1.79–2.77) Increasing age—OR 1.01 (95% CI 1.00–1.02) Alcohol—OR 2.58 (95% CI 1.55–4.29) Illicit drug problems—OR 1.89 (95% CI 1.09–3.25) Obesity—OR 1.38 (95% CI 1.13–1.69)	No difference in congenital heart anomalies in children born to women with different antidepressant prescribing exposure status; increased risk for congenital heart anomalies in children of older women, in children of women with diabetes, body mass index >30 kg/m^2, with history of alcohol and illicit drug problems independent of the prescription of antidepressants

aOR=adjusted odds ratio; aRR=adjusted relative risk; CHD=congenital heart disease; CI=confidence interval; OR=odds ratio; RR=relative risk; SSRI=selective serotonin reuptake inhibitor.

cardiac malformations (relative risk [RR], 1.36; 95% CI, 1.08–1.71) and septal defects (RR, 1.40; 95% CI, 1.10–1.77). The authors concluded that although the RRs were statistically significant, none reached clinically significant levels. (25)

The inconsistency across these studies may potentially be explained by differences in study design, or by confounding factors, such as maternal obesity, diabetes, or coadministered medications.

STUDIES THAT DEMONSTRATE NO TERATOGENICITY WITH SSRI USE

The balance of prospective studies and meta-analyses suggest no increased risk of teratogenicity and SSRI use. In a prospective, controlled, multicenter cohort study, mothers who contacted a teratology information service regarding the use of SSRIs were followed through their pregnancies (N=267). (15) The incidence of malformations in children born to women taking SSRIs was 4.1%, comparable to that found in the unexposed control subjects at 3.8%. The Norwegian Mother and Child Cohort Study (N=63,395) assessed infant outcomes following in utero SSRI exposure after adjusting for maternal depression, and found no increased risk of congenital malformations (5.6%) or cardiac defects (1.3%) compared with the unexposed control population at 4.6% and 0.9%, respectively. (19)

A study from Swedish national health registers that prospectively collected data on congenital malformations from 1996 to 2011 (N=70,339) found no statistically significant association between exposure to SSRIs and any relatively severe major congenital malformations (3.2%; OR, 0.94; 95% CI, 0.87–1.01), cardiac defects (1.1%; OR, 0.92; 95% CI, 0.81–1.05), or cardiac septal defects (0.78%; OR, 0.94; 95% CI, 0.80–1.14). (26)

Furthermore, a recent register-based prospective study from Sweden that included 17,736 infants exposed to SSRIs in utero found the same risk of total malformations (2.2%), cardiac defects (0.8%), and infant mortality within 28 days of birth (0.1%) compared to no SSRI exposure. (23) A nested cohort study using US Medicaid claims data (N=949,504) was consistent with the previously mentioned studies, with no increase in any cardiac malformation associated with prescription of an SSRI during the first trimester of pregnancy after adjustment for maternal illness (0.9% exposed vs 0.7% nonexposed; adjusted RR, 1.06; 95% CI, 0.93–1.22). (27)

A 2006 meta-analysis on SSRIs and pregnancy reported no difference for major malformations (OR, 1.39; 95% CI, 0.91–2.15) and cardiovascular malformations (OR, 1.19; 95% CI, 0.53–2.68). (28) A meta-analysis of 4 prospective cohort studies published in 2015 reported that there was no increased risk for presumed exposure to SSRIs and congenital cardiac defects combined, with a pooled adjusted OR of 1.06 (95% CI, 0.94–1.18). (29)

NEONATAL ADAPTATION

Poor neonatal adjustment syndrome, *neonatal behavioral syndrome*, or *neonatal abstinence syndrome* are used interchangeably to describe a constellation of signs and symptoms that occur after in utero exposure to SSRI; toxicity and withdrawal are both potential explanations for this syndrome. (30) Multiple scoring systems have been developed to evaluate the severity of neonatal withdrawal to opiates and other substances (31)(32)(33); these scoring systems have been successfully translated to SSRI exposure. The Finnegan scoring system is one of the most widely used and comprises signs and symptoms that reflect different disturbances within the central nervous system, as well as the vasomotor, gastrointestinal, metabolic, and respiratory systems. Large cohort studies have consistently demonstrated an increased risk of developing neonatal abstinence syndrome with third-trimester use of SSRIs.

One study examined poor neonatal adaptation in 247 infants exposed to SSRIs in the third trimester who were admitted for observation after delivery. (34) Poor neonatal adaptation was defined as having a Finnegan score of at least 4 on 1 occasion during the 72-hour observation period. There were 187 infants with exposure to an SSRI; for all SSRIs combined, 127 infants had poor neonatal adaptation, but only 5 required a NICU admission. Formula feeding was associated with an increased risk of poor neonatal adaptation compared with breastfeeding or mixed feeding (OR, 3.16; 95% CI, 1.40–7.13; *P*=.003).

Another study associated SSRI exposure during pregnancy with poorer self-regulation and higher levels of arousal in infants during the first month after birth. (35) No association was found with admission to a NICU.

TABLE 3. **SSRI Use and Breastfeeding**

ANTIDEPRESSANT	SOURCE		
	MALONE ET AL (36)	ACOG (37)	LACTMED (38)
Paroxetine	L2[a]	L2	Occasional mild side effects such as insomnia, restlessness and increased crying. One of the preferred SSRIs.
Fluvoxamine	Not applicable	L2	Doses of up to 300 mg daily would not be expected to cause any adverse effects.
Escitalopram	Not applicable	L3 in older infants	Doses up to 20 mg daily would not be expected to cause any adverse effects.
Citalopram	L3	L3	Few cases of minor behavioral side effects such as drowsiness. No adverse effects on development. Not a first choice.
Sertraline	L2	L2	Rarely, preterm infants with impaired metabolic activity might accumulate the drug and demonstrate symptoms similar to neonatal abstinence. One of the preferred SSRIs.
Fluoxetine	L2 in older infants L3 if used in neonatal period	L2 in older infants L3 if used in neonatal period	Adverse effects such as colic, fussiness, and drowsiness have been reported. Not a first choice.

ACOG=American Congress of Obstetricians and Gynecologists; SSRI=selective serotonin reuptake inhibitor.

[a] Lactation risk categories: L1, safest; L2, safer; L3, moderately safe; L4, possibly hazardous; L5, contraindicated. (39)

Overall, as studies demonstrate a heightened risk for neonatal adaptation syndrome, neonates exposed prenatally to SSRIs should be evaluated for signs of adverse effects. However, the incidence and severity of these effects do not appear to be so frequent or severe that women should avoid using these medications if they are otherwise indicated. (40)

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

PPHN is a syndrome characterized by the presence of high pulmonary vascular resistance and right-to-left shunting. Contrary to the primary pulmonary arterial hypertension of the adult, the syndrome of the newborn is not defined by a specific pressure of the pulmonary circulation. Hypoxia with right-to-left shunt and absence of congenital anomalies of the heart confirms the diagnosis. An increase in PPHN associated with late (41) or early (42) exposure to SSRIs has been reported in 2 studies; other studies have not found an association. (43)(44)(45) In July 2006, the US Food and Drug Administration (FDA) issued a public health advisory about a possible link between in utero exposure to SSRIs and PPHN. (46) Subsequently, in December 2011, the FDA issued a drug safety communication that retracted this warning. (47) The FDA stated that the initial public health advisory in July 2006 about this potential risk was based on a single published study. Since then, conflicting findings have been seen in newer studies evaluating this potential risk, making it unclear whether the use of SSRIs during pregnancy can cause PPHN. The FDA concluded that given the conflicting results from different studies, it was premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN. After the publication of the FDA statement, a multinational record-linkage study reported an increase in PPHN in offspring born to women who had filled a prescription for an SSRI late in pregnancy, with an aOR of 2.1 (95% CI, 1.5–3.0). (48)

Since then, a meta-analysis of 7 studies published through 2012 concluded that third-trimester exposure to SSRIs as a group was associated with PPHN (OR, 2.50; 95% CI, 1.32–4.73; P=.005), while first-trimester exposure was not (OR, 1.23; 95% CI, 0.58–2.60; P=.58). (49) Norby et al found that the rate of PPHN was increased in preterm and term infants exposed during pregnancy to SSRIs. (23) For term infants only, the rate of PPHN was higher with exposure in the third trimester compared with exposure in the first or second trimester only, with the number needed to harm of 285. It appears that there is an association between third-trimester SSRI use and PPHN, but the association is weak (OR, 2.50). Clinicians should weigh the risks and benefits of SSRIs and this weak association with PPHN against the primary obligation to maintain maternal mood stability.

BREASTFEEDING

All SSRIs cross the blood-milk barrier and are excreted in breast milk, with an estimated relative infant dose less than 2% of weight-adjusted maternal dose. (50) SSRIs have different safety profiles with breastfeeding (Table 3). Fluoxetine and citalopram are excreted in larger amounts, reaching infant plasma levels that can exceed 10% of the maternal concentration. (51)(52) Conversely, the relative infant doses are low for fluvoxamine, paroxetine, and sertraline. (51) Adverse events in breastfed infants exposed to SSRIs through breast milk have been suspected in a few cases, more often with fluoxetine and citalopram. (52) For example, crying, irritability, decreased feeding, and diarrhea have been reported for fluoxetine, (38)(52)(53)(54)(55) while hypotonia, colic, decreased feeding, and sleep difficulties have been described for citalopram. (52)(56)(57) Some studies suggest avoidance of these drugs in the medication-naïve postpartum patient. (38)(50)(57) However, if the neonate was exposed to these antidepressants in utero, the impact of postnatal exposure through milk is much lower and breastfeeding is recommended. (38)(50)(52)

Furthermore, breastfeeding has consistently been shown to mitigate neonatal adaptation symptoms faster than formula feeding in infants exposed to SSRIs during the third trimester of pregnancy. The well-documented advantages of breastfeeding (eg, nutritional, immunologic) appear to outweigh the potential risks of SSRI use during breastfeeding. (58) Given this, both the American Academy of Pediatrics (49) and the National Institutes of Health (46) consider SSRIs compatible with breastfeeding.

CONCLUSION

The choice to initiate SSRI treatment during pregnancy must be individualized for each patient, and include a discussion with her clinician, weighing the risks, benefits, and alternatives. With regard to teratogenicity, studies vary in quality and design, but large prospective studies suggest an overall minimal increased risk to first-trimester exposure to an SSRI. From a neonatal standpoint, familiarity with potential conditions associated with antenatal exposure to SSRIs, including poor neonatal adaptation and PPHN, can guide patient counseling if medication is initiated, and improve postnatal detection and management. Given that untreated maternal depression is associated with poor compliance to care and adverse perinatal outcomes, the balance of guidelines favor the initiation and continuation of SSRIs during pregnancy and the postpartum period when indicated.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the effects on the fetus and/or newborn infant of maternal psychiatric disorders and their treatment.

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Selective Serotonin Reuptake Inhibitor Use in Pregnancy: Repercussions on the Oblivious Passenger

Javier Rodriguez-Kovacs, Shelly H. Tien and Beth A. Plunkett

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Index of Suspicion in the Nursery

1 A Newborn with Absence of Right Forearm, Preauricular Pit, and an Infantile Hemangioma

Akhila Reddy Mandadi, MD,* Carlos Castillo, MD,* Magda Mendez, MD,*
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AUTHOR DISCLOSURE Drs Reddy Mandadi, Castillo, Mendez, and Rajegowda have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

CASE PRESENTATION

A female infant is born at 35 weeks' gestation to a 19-year-old Hispanic woman and a 21-year-old Hispanic man. The infant has a birthweight of 2,710 g (10th–25th percentile), length of 46.5 cm (10th–25th percentile), and head circumference of 34.1 cm (10th–25th percentile). Apgar scores at 1 and 5 minutes are 9 and 9, respectively. Her physical examination is remarkable for bilateral ear pits, absence of distal two-thirds of the right forearm and hand, and a stump with rudimentary fingers (Fig 1). Good range of motion was observed at the right elbow and shoulder. The left upper extremity and both lower extremities are normal. All her limbs have a good range of motion. No other dysmorphic features are present and the rest of her physical examination findings are unremarkable. A right extremity radiograph shows congenital absence of the right hand, with hypoplastic right forearm bones and a normal right humerus (Fig 2). Her nursery stay is uneventful and the patient is discharged with her mother.

The antenatal period had been uncomplicated and all maternal laboratory test results are unremarkable. Besides polycystic ovarian disease and a missed abortion 1 year before this pregnancy, the mother denies radiation exposure, trauma, medications, or chorionic villous sampling. The family history is negative for congenital anomalies but the father has bilateral ear pits as well. Prenatal ultrasonography at 7, 21, and 33 weeks did not identify any fetal abnormalities. The placental pathology did not show any evidence of amniotic bands.

During the fourth month health supervision visit, a grade II/VI systolic ejection murmur is identified and echocardiography does not show any congenital abnormalities, pointing toward a functional heart murmur. A hemangioma measuring 1×1 cm of the left labia majora is present (Fig 1), with normal external genitalia and anal opening. No genitourinary abnormalities are found on renal and bladder ultrasonography.

A comprehensive metabolic panel and complete blood cell count are within normal limits. Her karyotype is 46,XX. Microarray testing shows absence of heterozygosity, which can be indicative of uniparental disomy. These genomic findings are considered to be of uncertain clinical significance.

At 18 months of age, the patient is growing and developing well and her multidisciplinary care includes genetics, cardiology, rehabilitation medicine, and general pediatrics.

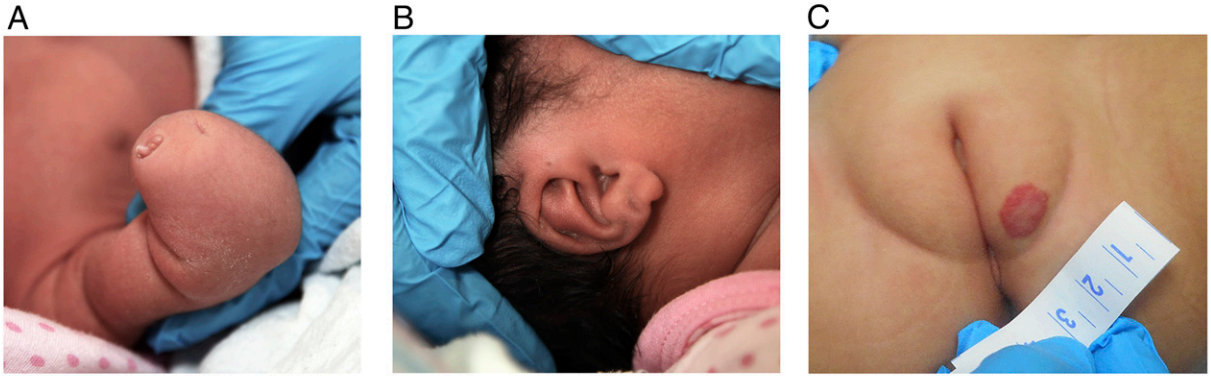

Figure 1. Physical findings seen in our patient. A. Hypoplastic right arm with absence of distal two-thirds of the right forearm and hand, with rudimentary fingers. B. Bilateral preauricular pits that were also present in the patient's father. C. A superficial hemangioma in the vaginal area.

DISCUSSION

Transverse limb defects (TLDs) are rare congenital abnormalities seen in approximately 3.5 to 6.9 per 100,000 births. (1) Most cases are sporadic and not associated with other abnormalities. Skeletal changes are commonly associated with vascular malformations while they are rarely seen in conjunction with hemangiomas. (2) To our knowledge, there has been no report to date of an association of TLD with perineal hemangioma and preauricular pits.

TLD is defined as a partial or complete absence of 1 or more fetal limbs beyond a certain point across the long axis. It is caused by disruption in the apical ectodermal ridge due to insults such as ischemia, bleeding, or chromosomal mutations, during the fourth to eighth week of gestation. One large study showed that the causes include vascular disruption in 35%, genetic factors in 24% of cases, aneuploidy in 6%, and teratogens in 4%, with 32% of cases being sporadic. (1) Other causes include chorionic villus sampling performed before the 10th week of gestation, maternal diabetes, and amniotic bands. Limb defects are not identified on prenatal ultrasonography in 45% of the cases. When multiple malformations are present, cardiovascular and urinary tract anomalies are common in combination with congenital limb defects (37% and 25% of cases), but digestive tract anomalies are significantly associated with congenital limb defects. Rare minor anomalies associated with TLDs include hemangiomas (<1% of cases) and ear malformation (<0.7% of cases). (3) Hemangiomas usually present in the neonate in the first 2 weeks and most commonly involve the head and neck area. Perineal hemangiomas are rare, and their presence should raise the suspicion of an underlying major anomaly. (4)

Multiple anomalies in this patient may be sporadic, vascular, or chromosomal in origin. As previously discussed, the presence of the 3 anomalies seen in our patient is extremely rare, raising the suspicion of a common etiology. Currently, well-known syndromes such as posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities (PHACE); spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization (SACRAL); and familial angiomatosis were reported initially as incidental findings in patients. This enhances the importance of further evaluation and close monitoring of our patient to identify other probable underlying abnormalities. Besides finding a cause, it is also important to address the consequences of an upper limb defect, including the psychological and physical effect in a developing child.

CONCLUSIONS

TLDs, ear pits, and perineal hemangiomas are commonly known to occur as isolated sporadic anomalies. The presence

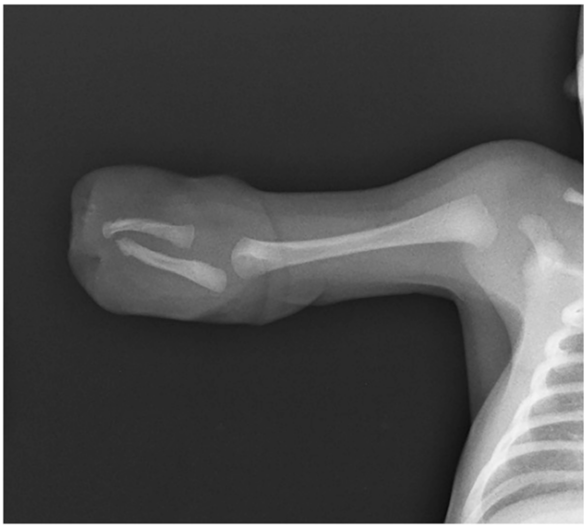

Figure 2. A right arm radiograph shows congenital absence of the right hand, with hypoplastic right forearm bones and a normal right humerus. The presence of radii in this patient can rule out other syndromes that present with limb defects.

of major and minor anomalies, should always raise the suspicion of other unidentified abnormalities

Lessons for the Clinician

The differential diagnosis of TLD can be multiple and often includes syndromes with multisystem involvement as follows:

- Thrombocytopenia absent radius syndrome: It is an inherited autosomal recessive disorder characterized by bilateral absence of radii with the presence of thumbs and thrombocytopenia. Hematologic findings may be absent and present within the first few weeks to months after birth.
- Adams-Oliver syndrome: The cardinal features are limb defects and aplasia cutis congenita.
- Fanconi anemia: Most of the cases are inherited in an autosomal recessive pattern. Laboratory findings include thrombocytopenia, macrocytosis, and anemia, but these findings can be absent in one-third of the cases. Absence of radii and hypoplastic thumbs are the most common physical findings.
- Cornelia de Lange syndrome: Despite having upper limb defects such as phalangeal abnormalities or oligodactyly, Cornelia de Lange syndrome is characterized by distinctive phenotypical features and growth restriction.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the clinical features and know how to diagnose and manage congenital anomalies of the upper extremities, such as syndactyly, polydactyly, absent clavicles, absent radius, Sprengel deformity, limb reduction.

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2 The Well-Appearing Cyanotic Infant

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AUTHOR DISCLOSURE Drs Krick, Kironde, and Hendrickson have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term male infant is born via spontaneous vaginal delivery at 40 2/7 weeks' gestational age to a gravida 2 para 2 mother. Her pregnancy was complicated by maternal tobacco use and inadequately treated group B *Streptococcus* colonization. The infant is vigorous at birth with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. The infant has growth parameters appropriate for gestational age and examination in the delivery room reveals bilateral clubfeet, but is otherwise normal.

At 11 hours of age, the infant is noted to have cyanosis with breastfeeding and is found to have an oxygen saturation of 83% measured in the right upper extremity with pulse oximetry. His breathing is unlabored and lung sounds are clear to auscultation. Heart rate and rhythm are normal and no murmurs are appreciated. Blood pressures in all 4 limbs, peripheral pulses, and perfusion are also all appropriate.

The infant receives oxygen supplementation via nasal cannula, which is subsequently escalated to nasal continuous positive airway pressure (CPAP) of 6 cm H_2O with a fraction of inspired oxygen (Fio_2) of 1.00. Despite these interventions, his pulse oximetry saturations remain between 70% and 80%. Chest radiography reveals a normal cardiac size and silhouette, with clear bilateral lung fields. A complete blood cell count with differential and blood glucose concentrations is also unremarkable. Blood culture specimens are obtained and the infant starts broad-spectrum antibiotics for empirical treatment of possible early-onset neonatal sepsis.

Given the concern for congenital cyanotic heart disease, the infant is transported via air ambulance to our tertiary care children's hospital. Echocardiography performed on admission at 16 hours of age reveals normal ventricular size and function, as well as an expected patent ductus arteriosus and foramen ovale with small left-to-right shunt. An arterial blood gas measurement is obtained while the patient is receiving an Fio_2 of 1.00, which reveals a partial pressure of arterial oxygen (Pao_2) of 279 mm Hg, while the measured oxygen saturation via pulse oximeter on the right upper extremity reads only 78%. The remainder of the blood gas value is within normal limits. Repeat arterial blood gas measured while the patient is breathing room air shows a Pao_2 of 73 mm Hg.

In the midst of the medical workup, the patient's mother and maternal grandfather arrive. A detailed family history is obtained and the team learns that the infant's mother herself was hospitalized in the NICU shortly after birth for cyanosis that persisted until 5 weeks of age. The patient's grandfather states that the mother was later diagnosed with a novel fetal hemoglobinopathy that resolved over time. Her diagnosis is subsequently confirmed and a presumptive diagnosis for the patient is made.

DISCUSSION

Diagnosis

The differential diagnosis for cyanosis in a newborn is broad, but it can be delineated into 2 major categories: conditions that result in deoxygenated hemoglobin and those that are due to an abnormality in the hemoglobin molecule itself. (1) Often a first diagnostic step, the hyperoxia test is a simple clinical test that can be helpful in differentiating cardiac etiologies of hypoxemia from other causes, such as pulmonary or hematologic. For the patient in the current case, because of the presence of a high Pao_2 with a low pulse oximetry reading in the setting of an Fio_2 of 1.00, along with a normal echocardiogram and cardiac examination, it is unlikely that his cyanosis is of a cardiac or pulmonary origin. With the added family history, there is a high index of suspicion for the presence of a hemoglobinopathy, specifically a methemoglobinemia. On further review of the mother's records, it is determined that she was diagnosed with Hb FM-Fort Ripley, a fetal hemoglobinopathy. Based on this information, a presumptive diagnosis is made, "which is later confirmed by the newborn screen (Fig)." The nasal CPAP is discontinued and the infant is discharged from the hospital and continues to receive close follow-up. Over the course of the next 2 months, his cyanosis completely resolves.

The Condition

Methemoglobinemia is a rare cause of cyanosis in neonates. Methemoglobin is the altered state of hemoglobin that occurs when the ferrous iron (Fe^{2+}) is oxidized to its ferric state (Fe^{3+}) within the heme moiety of hemoglobin. (1) Heme in the ferric state is unable to carry oxygen and leads to the clinical finding of cyanosis. (2)

Methemoglobinemia can be acquired or congenital. Acquired methemoglobinemia can be caused by a number of medications and commercially available chemicals. Acquired methemoglobinemia ranges in severity, but can be life threatening and require acute management. (3)

Congenital methemoglobinemia is very rare and can be caused by deficiencies in an essential methemoglobin reduction enzyme (NADH-cytochrome b5 reductase) or its cofactors, or by abnormal hemoglobin variants. (3) In such cases of abnormal hemoglobin variants, known as M hemoglobins, abnormalities can be found in the α-globin, β-globin, or γ-globin chains. Most patients with hemoglobin M disease are asymptomatic and, in contrast to acquired methemoglobinemia, typically do not have any clinical sequelae and do not require any therapeutic interventions.

Depending on the globin chain affected, cyanosis from hemoglobin M disease may be present at different stages of life. In disorders in which the α-globin chain is affected, cyanosis may appear at any time, because this globin chain is present in both adult and fetal hemoglobins. In disorders affecting the γ-globin chain, cyanosis will appear during the neonatal period and will be transient, resolving when the γ-globin is replaced by β-globin and adult hemoglobin is formed. As such, when the β-globin chain is affected, cyanosis will not appear until a few months after birth when adult hemoglobin has replaced fetal hemoglobin.

Hb FM-Fort Ripley is caused by a single amino acid substitution causing a mutant γ-globin chain, leading to a

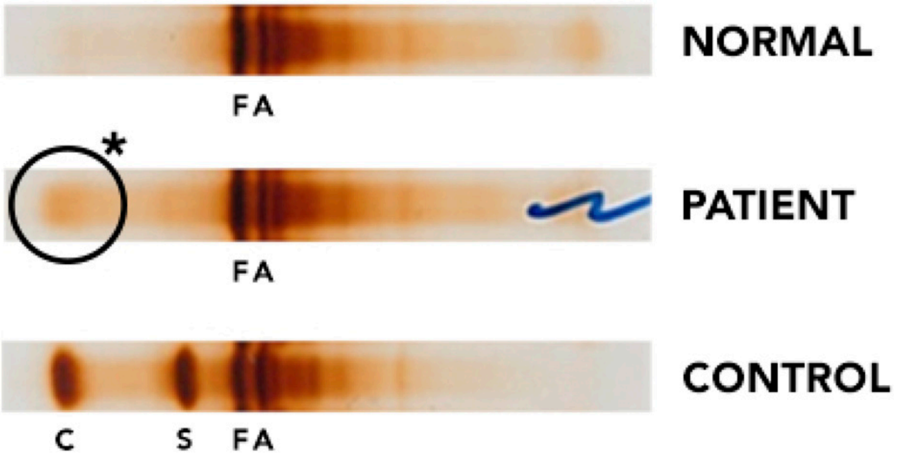

Figure. Isoelectric focusing (IEF) from newborn screen performed by the Washington State Newborn Screening Lab. The hemoglobin variant (*) was picked up on the initial IEF test. The variant band is washed out in the Hb C region and did not fully resolve. The hemoglobin variant was highly unstable and was absent on repeat confirmatory testing and so the newborn screen was reported as normal. C=Hb C; S=sickle Hb; F=fetal Hb; A=adult hemoglobin.

functionally abnormal fetal hemoglobin molecule and congenital methemoglobinemia. (4) Because the heme iron remains in the ferric state, it cannot carry oxygen and is relatively resistant to reduction by NADH-cytochrome b5 reductase. (5) This causes slightly elevated methemoglobin levels in affected patients, leading to the primary finding of cyanosis. As it affects the γ-globin chain, it leads to cyanosis exclusively within the first few months of age and gradually improves over time as fetal hemoglobin is replaced by adult hemoglobin. (2)

Hb FM-Fort Ripley has an autosomal dominant inheritance pattern with incomplete penetrance. (6) Such a variant in the γ-globin chain may go undetected on newborn screening because of its unstable nature. The diagnosis of Hb FM-Fort Ripley has been made in some familial cases by next-generation sequencing, where a missense mutation in a single codon was found to be the source of the variant. (7)

Management

Cyanosis in patients with Hb FM-Fort Ripley typically resolves over the first few months of age with the transition to adult hemoglobin. Patients affected by this condition, as well as those with other M hemoglobins who have only mild elevations in methemoglobin levels, are typically asymptomatic. For most patients, there is no clinical sequela and no treatment is required.

Given the rarity of the condition and the challenges of quickly identifying this particular congenital methemoglobinemia, a detailed family history was key to making the diagnosis in a timely manner. Early diagnosis may allow clinicians to pursue fewer interventions after the exclusion of more serious and harmful etiologic factors. Our patient was discharged from the hospital with instructions to follow up with hematology for expectant management of the disease.

Lessons for the Clinician

- The differential diagnosis for cyanosis in a neonate is broad and should consider both disorders that lead to deoxygenated hemoglobin and those that are due to an abnormality involving the hemoglobin molecule itself.
- Methemoglobinemia can be congenital or acquired and differ in management.
- Hemoglobin M disorders can cause cyanosis at different ages, depending on the globin chain affected.
- Obtaining a family history, including the birth history of close relatives, can be critical to the diagnosis of rare conditions in neonates.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the biochemical characteristics of fetal hemoglobin.
- Know the clinical and laboratory features of neonatal hemoglobinopathies, including the thalassemias.
- Know the indications for and approaches to screening for hemoglobinopathies in the newborn population.

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Case 2: The Well-Appearing Cyanotic Infant

Jeanne A. Krick, Tendo Kironde and Melinda Hendrickson

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3 Neonate with Sudden Onset of Hypotonia on the Second Day After Birth

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PRESENTATION

A 2-day-old 3-kg female term neonate is born in a normal vaginal delivery with Apgar scores of 8, 8, and 9 at 1, 5, and 10 minutes, respectively. During morning rounds, she is noted to have a weak cry. Antenatal and natal history findings are normal. Detailed neurologic examination shows a fully conscious neonate with decreased shoulder tone and head lag. Neonatal reflexes are also diminished, with a weak cry, poor swallowing, and poor sucking reflex. There are no clinical features of respiratory distress or respiratory failure, shock, seizure, or altered sensorium. The neonate is evaluated with a sepsis screen, serum glucose, serum calcium, serum electrolytes, and serum magnesium for neonatal sepsis or metabolic derangements. Laboratory investigation shows normal sepsis screen and metabolic evaluation (total white blood cell count of 13,000/μL [13×10^9/L], C-reactive protein level of 0.01 mg/L [0.10 nmol/L], serum glucose of 89 mg/dL [4.9 mmol/L], total serum calcium of 8.4 mg/dL [2.1 mmol/L], ionized calcium of 4.6 mg/dL [1.1 mmol/L], serum magnesium of 1.3 mEq/L [0.65 mmol/L], serum sodium of 138 mEq/L [138 mmol/L], and serum potassium of 4.6 mEq/L [4.6 mmol/L]). Head neurosonography to rule out any bleeding or malformations has normal findings but neonatal hypotonia persists. At this time, one investigation clinches the diagnosis.

DISCUSSION

In a neonate with sudden onset of hypotonia, the initial differential diagnosis includes neonatal sepsis; metabolic derangements such as hypermagnesemia, hypocalcemia, and hypokalemia; antibiotic toxicity due to aminoglycosides; botulism; and cerebral malformations or bleeding. The neonate was evaluated for metabolic causes and neonatal sepsis, and the investigation showed normal sepsis screen and metabolic profile, thus ruling out these causes. The infant had no history of receiving antibiotics and she was exclusively breastfed, thus ruling out elevated levels of aminoglycosides or infantile botulism as a cause. Head ultrasonography findings were normal, which ruled out bleeding or malformations as the cause. On taking a detailed antenatal and natal history again, the mother was found to have myasthenia gravis (MG), for which she was taking pyridostigmine for the past 5 years and was asymptomatic. The infant was evaluated with anticholinergic receptor antibodies. The infant was started on tube feedings and was observed for respiratory distress or failure or worsening of hypotonia, with monitoring of vital parameters. The laboratory results showed the presence of anticholinergic receptor antibodies with very high titers (8.8 mmol/L; normal range, 0–0.25 mmol/L), thus confirming a diagnosis of congenital MG.

Treatment

The neonate was started on oral pyridostigmine treatment (9 mg/kg per day) with continuation of tube feeding. She gradually showed improvement in muscle tone and on day 3 after starting treatment, she began breastfeeding. Her cry normalized and she was discharged on day 7 after birth. The infant was followed up regularly and treatment with pyridostigmine was stopped at age 4 weeks. The infant's muscle tone was appropriate for age at this time, and she received regular follow-up with no recurrence.

The Condition

MG is an autoimmune disease resulting secondary to the antibodies that are directed against the postsynaptic membrane of the neuromuscular junction. This leads to muscle weakness and easy fatigability of skeletal muscles.

Congenital MG is usually transient and results from transplacentally acquired antibodies of the mother. This condition is transient, therefore asymptomatic neonates require regular follow-up for early identification of hypotonia. If the neonate is symptomatic, as in the current case, then it is considered an indication for starting pharmacotherapy. The infant recovers as the effect of antibodies wanes.

Congenital myasthenic syndromes (CMS) include heterogeneous genetic diseases that are characterized by defective neuromuscular transmission. CMS can be classified as presynaptic, synaptic, or postsynaptic, depending on the primary defect's location within the neuromuscular junction. Difficulty in limb movement and associated hypotonia in a neonate are usually secondary to the neuromuscular junction disorder. Neuromuscular transmission is defective, finally leading to muscle exhaustion and decrease in tone. Most cases of CMS are transient and neonates gradually recover as the effects of antibodies wears off, but in a few cases, CMS is lifelong. Transient neonatal MG (TNMG) is usually seen in approximately 10% to 20% of neonates whose mothers are affected by MG. (1) Most of these mothers have clinically active manifestations of MG, but occasionally, the mother may be in the remission phase before the birth, thus making it difficult to suspect TNMG as in the current case. (2)

MG is classified as an autoimmune disorder in which acetylcholine receptor (AChR) antibodies are directed against the AChR of the neuromuscular junction. These antibodies thus block the receptors of acetylcholine, and affect postsynaptic neuromuscular transmission. (3) Maternal AChRs are transferred in utero and these antibodies are responsible for the TNMG seen in these neonates. (1) (4) The recurrence risk of TNMG, if a previous neonate was affected, is up to 70% to 75% in the next pregnancy. TNMG is of 2 types, namely, seronegative MG and seropositive MG. In seronegative MG, the diagnosis is made only on clinical, electrophysiological, and pharmacological bases, and AChR antibodies are absent, whereas in seropositive MG, AChR antibodies are present in high titers, as in the current case.

Clinical Features

TNMG typically presents within the first few hours after birth (never reported after day 3 after birth) with definite signs being seen by the third day of postnatal age. (5) More severely affected infants have a history of polyhydramnios in utero and may present with arthrogryposis multiplexa at birth. Infants with TNMG have generalized weakness and hypotonia with typical presence of deep tendon reflexes. (4) Facial diplegia is seen commonly, and in contrast to MG seen in adults, ptosis and ophthalmoplegia occur less frequently. Bulbar weakness is frequent, leading to poor sucking, swallowing, and a weak cry. Pooling of secretions and respiratory muscle weakness may lead to respiratory failure requiring ventilatory support. (1)

Diagnosis

TNMG should be suspected in a neonate whose mother is diagnosed with MG. If the mother does not have MG, the diagnostic test result is the response of the infant to administration of an anticholinesterase inhibitor. The agent used most commonly is neostigmine methylsulfate (0.15 mg/kg intramuscular or subcutaneous). The result is considered positive when clinical improvement is noted in roughly 15 minutes and continues for 1 to 3 hours. Atropine may be needed to control muscarinic side effects such as diarrhea and increased tracheal secretions. This test should be conducted in a hospital setting where resuscitation facilities are available. Intraventricular hemorrhage or hypoxic-ischemic encephalopathy may occasionally interfere with an infant's response to the administration of an anticholinesterase inhibitor. In these conditions, repetitive nerve stimulation is provided to support the diagnosis. (6) This test compares the amplitude of the fifth evoked compound muscle action potential to the first, before and after administration of an anticholinesterase-inhibiting agent. A positive response is a reduction of the fifth action potential by 10% or more and reversal of this decrement by the anticholinesterase inhibitor. (1)

Management

Management for neonatal myasthenia is mainly supportive. Small frequent feedings are provided by nasogastric or orogastric tube, and assistive ventilation is given if required. In addition, neostigmine methylsulfate (0.05 to 0.1 mg/kg intramuscular or subcutaneous) is given 30 minutes before each feeding. When feeding and respiratory abnormalities improve, neostigmine is given orally (0.5 to 1.0 mg/kg approximately 45 minutes before eating). Excessive doses may result in increased secretions, diarrhea, weakness, and muscle fasciculations. Pyridostigmine can also be used as an alternative drug. With continued clinical improvement, the dosage is decreased gradually. In addition, the course of the disease can be monitored with repeat nerve stimulation testing and measurement of AChR antibodies. Most patients (∼90%) recover fully before age 2 months. Tube feeding and assisted ventilation are rarely required for more than 1 to 2 weeks, with the drug being required for an average duration of 4 weeks. (7)(8)(9)

Lessons for the Clinician

- Transient neonatal myasthenia gravis is an infrequently seen condition.
- All neonates born to mothers with myasthenia gravis need to be monitored closely for clinical manifestations of neonatal myasthenia gravis.
- Treatment is with the administration of anticholinesterase inhibitor and usually is needed for 4 to 6 weeks.
- Prognosis is excellent, with most neonates improving with no sequelae.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the basis for (including genetic) and clinical and laboratory features (including associated abnormalities), differential diagnosis, management, and outcomes of neonatal hypotonia/neuromuscular weakness.

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Parent Resources from the AAP at HealthyChildren.org

- Pulse Oximetry Screening to Detect Newborn Congenital Heart Disease https://www.healthychildren.org/English/ages-stages/baby/Pages/Newborn-Pulse-Oximetry-Screening-to-Detect-Critical-Congenital-Heart-Disease.aspx
- Depression During & After Pregnancy: You Are Not Alone https://www.healthychildren.org/English/ages-stages/prenatal/delivery-beyond/Pages/Understaning-Motherhood-and-Mood-Baby-Blues-and-Beyond.aspx
- Birthmarks & Hemangiomas https://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Birhtmark-Hemangiomas.aspx
- Finally- Delivery Day! https://www.healthychildren.org/English/ages-stages/prenatal/delivery-beyond/Pages/Finally-Delivery-Day.aspx

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at http://patiented.aap.org.

Case 3: Neonate with Sudden Onset of Hypotonia on the Second Day After Birth

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An Infant with an Omphalocele Ends Up with Organ Transplants

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AUTHOR DISCLOSURE Dr Sims has disclosed that she has been compensated for reviewing records and providing testimony in some of the cases highlighted in Legal Briefs. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A 2,226-g female infant with a prenatal diagnosis of an omphalocele was born at 33 3/7 weeks' gestation to a 43-year-old gravida 4, para 1, aborta 3 woman. The pregnancy was unremarkable except for the known abdominal defect containing a portion of the liver and preterm labor. Before delivery, the woman had received nifedipine for tocolysis, antibiotics as a result of preterm labor, and 1 dose of antenatal steroids. However, labor progressed and the infant was born via cesarean delivery. The infant emerged active and had Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. A loose nuchal cord was noted at delivery. The umbilical cord gases were normal. The physical examination showed a normal-appearing infant with a soft abdomen without distention and an omphalocele. The surgery team determined that a silo was not necessary because the defect was "small," with only a portion of the liver as the contents in the sac, and a "large abdominal domain." The neonatology team covered the omphalocele with xeroform and placed a Replogle tube and peripheral intravenous line. Echocardiography and ultrasonography of the head were performed, and no cardiac or brain abnormalities were found.

Fifteen hours after birth, the infant was brought to the operating room (OR) for omphalocele excision with reduction and primary closure. During the 3½ hours in the OR, the surgeons noted that the abdominal cavity was actually too small to fit the large anterior lobe of the liver that was within the sac. Because of this complication, the surgical team digitally stretched the abdomen to provide more space to accommodate the entire liver. During the procedure, a small amount of bleeding occurred on the inferior border of the liver segment, which was compressed with gauze. When the bleeding stopped, the anterior lobe of the liver was then pushed into the abdominal cavity.

Within an hour after returning to the NICU from the OR, the infant's blood pressure (BP) began to decrease. The neonatologist was informed and ordered a blood gas measurement. The capillary gas showed a pH of 7.05, partial pressure of carbon dioxide of 73 mm Hg (9.7 kPa), partial pressure of oxygen of 36 mm Hg (4.8 kPa), and base excess of -12. The hypotension continued. Six hours after returning from the OR, the infant remained intubated and had a BP of 33/18 mm Hg with a mean of 23 mm Hg. The nurse noted that the infant had not voided since the operation. The neonatologist ordered normal saline boluses, initiated inotropic support, and administered bicarbonate boluses. Repeat capillary blood gases continued to show similar base deficits despite these measures. The neonatologist ordered renal ultrasonography, which showed decreased perfusion of the right kidney compared to the left. The nurse noted that the lower extremities were becoming poorly perfused. The neonatologist left messages for the surgical resident and attending physician about the lack of urine output, persistent hypotension, metabolic acidosis, decreased perfusion to the lower extremities, and decreased renal perfusion noted on ultrasonography. The surgeons did not return the calls. The nurse and the pediatric resident continued through the night leaving messages for the surgeons. The attending neonatologist went to bed with instructions to continue to call the surgeons and order more fluid boluses, additional bicarbonate boluses, increase the inotropic support, and increase the ventilator settings. ***The plaintiff surgeon was critical of the lack of response from the surgeon and the plaintiff neonatologist was critical of the abdication of responsibility of the treating neonatologist.***

The bedside nurse did not notify the charge nurse of the situation and she and the pediatric resident followed the instructions of the neonatologist. ***On deposition, the neonatologist said he could do nothing further without the surgeon's evaluation. The plaintiff was critical of this passive approach because the infant's clinical condition was deteriorating and there was no reasonable explanation or game plan. The bedside nurse said she could not do anything except to keep reminding the pediatric resident about the deterioration. The pediatric resident stated that whenever he phoned his supervising attending neonatologist, he was told to order additional fluid and bicarbonate boluses, increase the inotropic support, increase the ventilator settings, and continue to call the surgical resident. The plaintiff experts pointed out that these were bandages, and did not constitute an understanding of why the infant's condition was deteriorating after a presumably simple omphalocele repair nor was there a sensible plan to correct this infant's massive decompensation.***

By the early morning, 9 hours after the omphalocele surgery, the surgical resident came to the infant's bedside, and at the insistence of the mother, the surgical resident called the attending surgeon. ***The surgical resident explained on deposition that he had never cared for an infant with an abdominal wall defect and thought it was not appropriate to awaken his attending surgeon because he considered the medical team in charge of fixing the medical issues. The plaintiff experts pointed out that because of his lack of experience, he was obligated to call his supervisor.***

Twelve hours after surgery, the attending surgeon was at the infant's bedside. The infant continued to have metabolic acidosis, low blood pressures, and poor peripheral perfusion to the lower extremities. On physical examination, the abdomen was soft and nondistended but the site of the surgical wound was discolored and this discoloration began migrating to the groin. The attending surgeon ordered abdominal ultrasonography "to assess venous return" because of concern for "kinking" in the venous return to the heart. The scan showed: 1) absence of blood flow into the liver with no evidence of hepatic and portal venous flow; 2) absence of blood flow to the right kidney; 3) some blood flow to the splenic hilum; 4) mild ascites; and 5) lack of visualization of the inferior vena cava. The infant's BP and pH (6.9) continued to be low and the infant developed a mixed respiratory and metabolic acidosis. The infant's oxygen saturations began to decrease and total body edema became evident. The infant's ventilator settings, inspired oxygen, bicarbonate boluses, and pressor support were again increased. At this point, the attending surgeon left the bedside because he had a scheduled operation at another hospital. ***When the attending surgeon was asked why he left the infant's bedside that morning, he said that organs can usually withstand 8 hours of hypoxia or ischemia before becoming damaged, so he had time to do the other surgery. The plaintiff surgeon and neonatologist remarked that this was unconscionable.***

Later that day, 24 hours after the surgery, the attending surgeon returned to the bedside. Because the infant was extremely unstable, emergency surgery was performed at the bedside for abdominal decompression. When the abdomen was opened, the surgeon found liver volvulus and a nonviable 25-cm segment of distal ileum and right colon with several other segments of the bowel questionably viable. A silastic sheet was placed. ***When the surgeon was asked to explain the cause of this infant's deteriorating condition after surgery, he said that the possibilities in his mind at that point were: 1) "under-resuscitation" (ie, need for greater fluid resuscitation); 2) abdominal compartment syndrome in which the abdomen becomes subject to increased pressure, though he agreed that the lack of abdominal distention is not consistent with this theory; or 3) kinking of the liver. He said he was not concerned about bleeding because the abdomen was soft. He further added that he was not called in a timely manner. The surgical resident explained that he did not want to disturb his attending.*** The infant developed disseminated intravascular coagulopathy, elevated liver enzymes, and renal dysfunction. The infant required multiple transfusions of packed red blood cells, fresh frozen plasma, and cryoprecipitate to treat the coagulopathy.

Three days after birth, the infant was brought back to surgery to reexplore the questionably viable bowel. Additional bowel, as well as the central liver lobe and gallbladder, were found to be necrotic, necessitating removal. The infant had a stormy course consisting of liver and renal failure and short gut syndrome. She required prolonged parenteral nutrition, nasojejunal tube feedings, and hemodialysis, as well as a prolonged duration of assisted ventilation. She eventually received a small bowel, pancreas, and liver transplant. She developed feeding aversion and had developmental delays.

The plaintiff sued the hospital (surgical resident and nurse), neonatologist, and attending surgeon. The hospital was sued because the bedside nurse passively watched the deterioration of her patient without advocating for the safety of the infant. The plaintiff argued that it was not appropriate to continue to call the physicians without demanding a decisive and reasonable evaluation and management approach. In this situation, the plaintiff noted that she needed to go up the chain of command. The plaintiff sued the surgical resident because he needed to awaken his supervisor as he lacked the experience to choose to ignore the situation. The plaintiff sued the neonatologist because he passively watched as his patient's condition deteriorated. Instead, they offered that he had several options: leaving a message with the surgical team that if he did not hear back immediately, he would attempt to find another surgeon or call the chief of surgery at the hospital; if all of that failed, he needed to transfer the infant to another hospital. The attending surgeon was sued because he should have realized that the combination of large liver size and limited abdominal space probably caused a lobe of the liver to rotate; he also should not have abandoned his patient when he first saw the clinical deterioration 12 hours after the operation. He needed to closely monitor the evolving events, including awaiting the results of abdominal ultrasonography and operating in a timely manner to assess the internal findings. The defense contended that despite appropriate intervention, the inherent problem of an omphalocele carries risks and that nothing could have been done to prevent this situation. The plaintiff team pointed out that this was a simple omphalocele without associated anomalies. The fact that the infant was preterm underscored a probable limited abdominal domain, and pressure from the primary closure created havoc on all the organs.

The case settled without going to trial.

DISCUSSION

An omphalocele is an anterior abdominal wall defect at the base of the umbilical cord associated with herniation of the abdominal contents. The defect is covered by a domelike mesenchymal membrane composed of amnion and peritoneal membrane. The liver and small intestine usually occupy a portion of the sac, with other abdominal organs less likely to be present in the sac. The omphalocele results from a failure of the intestines to return to the abdominal cavity during weeks 6 to 10 of fetal development. Prenatally, this anomaly is detected during routine fetal ultrasonographic examination or occasionally with an elevated maternal α-fetoprotein concentration during prenatal screening. The incidence of omphalocele is 1 in 1,100 fetuses at around 14 to 18 weeks' gestation, but 1 in 4,000 to 6,000 infants; this discrepancy occurs because of a the high rate of pregnancy termination secondary to associated anomalies as well as secondary to fetal death and spontaneous abortion. Additional anomalies are found in up to 80% of fetuses with omphaloceles who have normal karyotypes. Chromosomal defects are noted in approximately 49% (mostly trisomy 13, 18, or 21, occasionally Turner and Klinefelter syndromes). Only 14% of omphaloceles are truly isolated. One-third of fetuses considered to have isolated omphalocele in utero actually have multiple associated defects detected postnatally. Other associations with omphalocele include VACTERL association (vertebral, anorectal, cardiovascular, tracheosophageal fistula, esophageal atresia, renal or radial anomalies, limb defect), Beckwith-Wiedemann syndrome (macrosomia, macroglossia, visceromegaly, hemihypertrophy, hypoglycemia, renal pathology), EEC syndrome (ectodermal dysplasia, ectrodactyly, cleft palate), and OEIS (omphalocele, exstrophy, imperforate anus, spinal defects), and triploidy syndromes. The male-to-female ratio is 1:1.

The differential diagnosis in a prenatal diagnosis of omphalocele includes the other major abdominal wall defect—gastroschisis. Gastroschisis involves herniation of the bowel through a small, off-midline (usually to the right) position but without the membrane covering, a feature that leaves the bowel vulnerable. The intestines are vulnerable because of exposure of the bowel serosa to amniotic fluid, and in particular, waste products in the fluid, including meconium. Most patients with gastroschisis are identified prenatally on ultrasonography or with elevated maternal α-fetoprotein levels, a finding that is more specific to a diagnosis of gastroschisis rather than an omphalocele. Gastroschisis occurs in 1 in 4,000 live births with the incidence steadily increasing over the last few decades. The etiology of gastrochisis is not known, but 2 theories have been suggested. One theory suggests that an involution of the right umbilical vein causes necrosis in the abdominal wall leading to a right-sided defect. The second theory postulates that premature involution of the right vitelline artery causes weakening in the abdominal wall through which intestinal contents subsequently rupture.

Risk factors for gastrochisis that have gained some attention, but are far from being validated, include exposure to external agents such as vasoconstricting decongestants, nonsteroidal anti-inflammatory agents, cocaine, and possibly pesticides/herbicides. The presence of associated defects is lower in patients with gastrochisis than those with omphalocele and has been reported to be 5% to 20%. The defects associated with gastrochisis are mostly intestinal atresias directly associated with ischemic or mechanical injury to the eviscerated bowel during gestation. The morbidity risks are related to the intestinal dysfunction after birth.

The neonatal management of abdominal wall defects involves appropriate fluids because of the significant evaporative losses. Gastric decompression is critical to prevent intestinal distention. The herniated tissues should be wrapped in warm saline-soaked gauze and then in plastic to reduce evaporative losses and temperature instability. For newborns with an omphalocele, a thorough search for associated anomalies should be undertaken, including cranial, cardiac, and renal ultrasound examinations. Depending on the associated anomalies and the size of the defect compared with the abdominal space, either a silo or primary closure is performed. These procedures help to minimize the risk of injury to the abdominal viscera either through direct trauma or as a result of increased intra-abdominal pressure. The deleterious effects of high intra-abdominal pressures have more recently led to a liberal use of temporary placement of a silo. Presized silos are now available and can be placed in the NICU. When staged closure cannot be tolerated, "escharatic therapy" (ie, epithelialization of the abdominal tissues) is used, especially in an infant with premature gestation, pulmonary hypoplasia, congenital heart disease, or other conditions precluding a staged reduction and closure.

The initial management for newborns with a gastrochisis is similar to that for an omphalocele with respect to fluids and gastric decompression. After being wrapped in warm saline-soaked gauze, the herniated bowel should be placed in a central position on the abdominal wall with the infant positioned on the right side to prevent kinking of the mesentery. It is important to perform a thorough evaluation to determine the coexistence of other anomalies. The bedside clinician should assess the bowel for evidence of an intestinal band, atresia, necrosis, or perforation. Surgical management ranges from staged reduction to primary reduction with operative closure. The prognosis in a newborn with an omphalocele is related to the severity of associated anomalies whereas the prognosis in a newborn with gastroschisis is primarily determined by the degree of bowel injury.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the approach to management, clinical manifestations, differential diagnosis, and complications of treatment of omphalocele in neonates.

Suggested Readings

Calzolari E, Bianchi F, Dolk H, Milan M; EUROCAT Working Group. Omphalocele and gastroschisis in Europe: a survey of 3 million births 1980-1990. *Am J Med Genet.* 1995;58(2):187–194

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Frolov P, Alali J, Klein MD. Clinical risk factors for gastroschisis and omphalocele in humans: a review of the literature. *Pediatr Surg Int.* 2010;26(12):1135–1148

Torfs CP, Katz EA, Bateson TF, Lam PK, Curry CJ. Maternal medications and environmental exposures as risk factors for gastroschisis. *Teratology.* 1996;54(2):84–92

Legal Briefs: An Infant with an Omphalocele Ends Up with Organ Transplants

Maureen E. Sims

NeoReviews 2018;19;e179
DOI: 10.1542/neo.19-3-e179

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Late-Term Induction of Labor

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal values for arterial umbilical cord gas values and indications of acidosis are defined in the Table.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

AUTHOR DISCLOSURE Drs Krasker and Golen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. Arterial Umbilical Cord Gas Values

	pH	Pco$_2$ (mm Hg)	Po$_2$ (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤−10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤−10
Metabolic acidosis	<7.20	<60	Variable	≥−10
Mixed acidosis	<7.20	>60	Variable	≥−10

*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695.

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:
  - Absent: Amplitude range is undetectable
  - Minimal: Amplitude range is greater than undetectable to 5 beats/min
  - Moderate: Amplitude range is 6–25 beats/min
  - Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate

  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - ■ Recurrent late decelerations
    - ■ Recurrent variable decelerations
    - ■ Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

History

A 33-year-old gravida 1, para 0 woman at 41 3/7 weeks' gestation was admitted to labor and delivery for a late-term induction of labor. She denied contractions, vaginal bleeding, or leaking fluid. She reported active fetal movement.

Her pregnancy course was uncomplicated, and she had no relevant medical or surgical history.

She underwent ultrasonography at 40 1/7 weeks' gestation which was notable for a biophysical profile of 8/8 and mild bilateral pyelectasis in the fetus which required postpartum follow-up.

Case Progression

On arrival at the labor and delivery department, she was comfortable and in no acute distress. Her examination findings were notable for a maternal heart rate of 91 beats/min and a blood pressure of 133/87 mm Hg. Bedside ultrasonography confirmed a fetus in the cephalic presentation. The initial FHR tracing is shown in Fig 1.

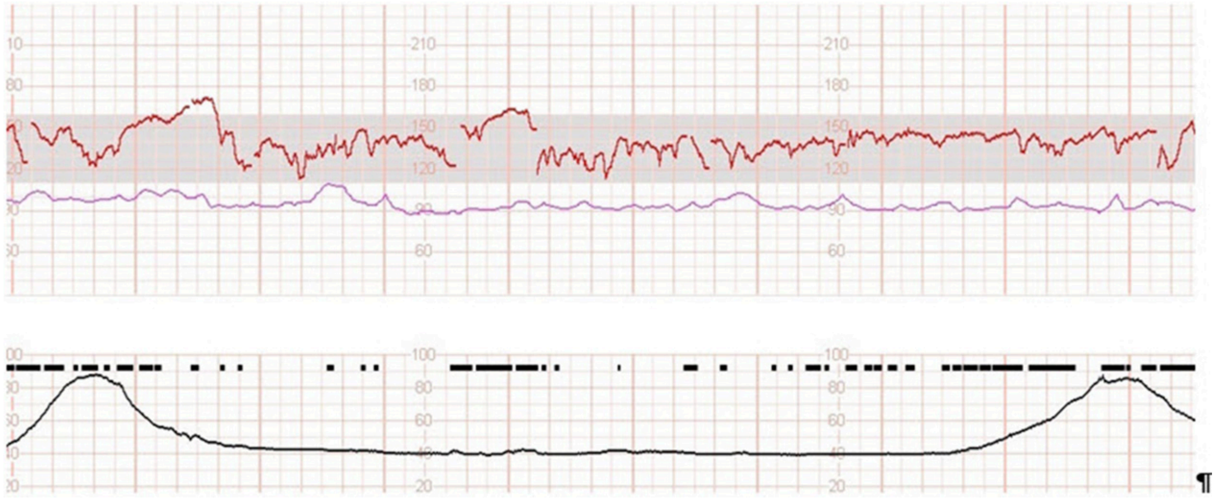

Figure 1. Electronic fetal monitoring strip 1.

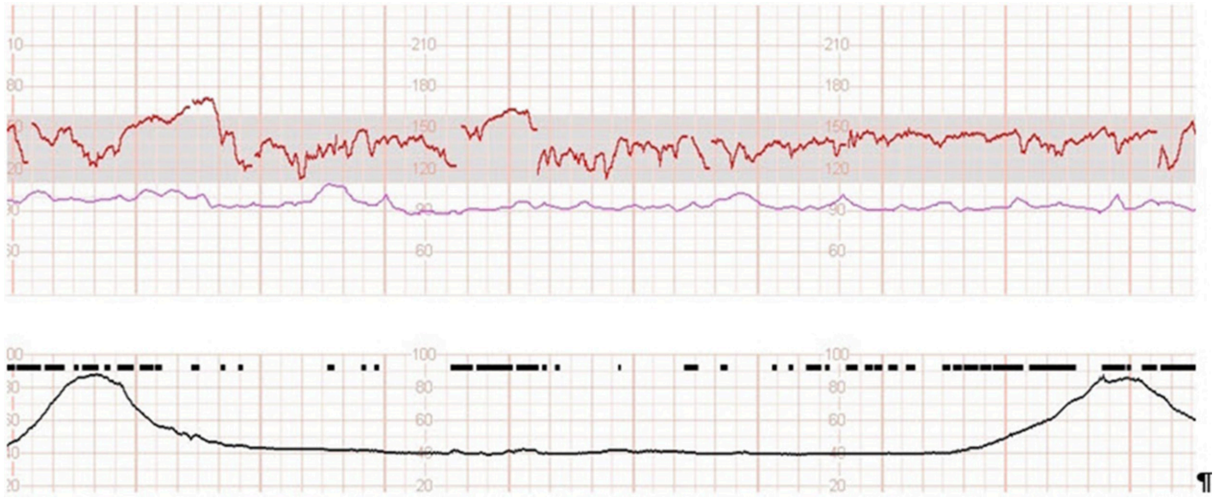

Figure 1. Electronic fetal monitoring strip 1.

Findings from EFM strip 1 are as follows:

- Variability: Moderate
- Baseline rate: 130 beats/min
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: Every 8 minutes
- Interpretation: Reactive nonstress test
- Differential diagnosis: Normal FHR tracing
- Action: Initiate induction of labor with misoprostol

A sterile vaginal examination was performed, and patient's cervix was found to be posterior. At that time, 25 μg of misoprostol was placed per vagina for induction of labor (day 1, 10:30 pm).

Four hours later, a second dose of 25 μg of misoprostol was placed (day 2, 2:30 am), following the protocol for induction of labor with misoprostol, given the FHR tracing shown in Fig 2.

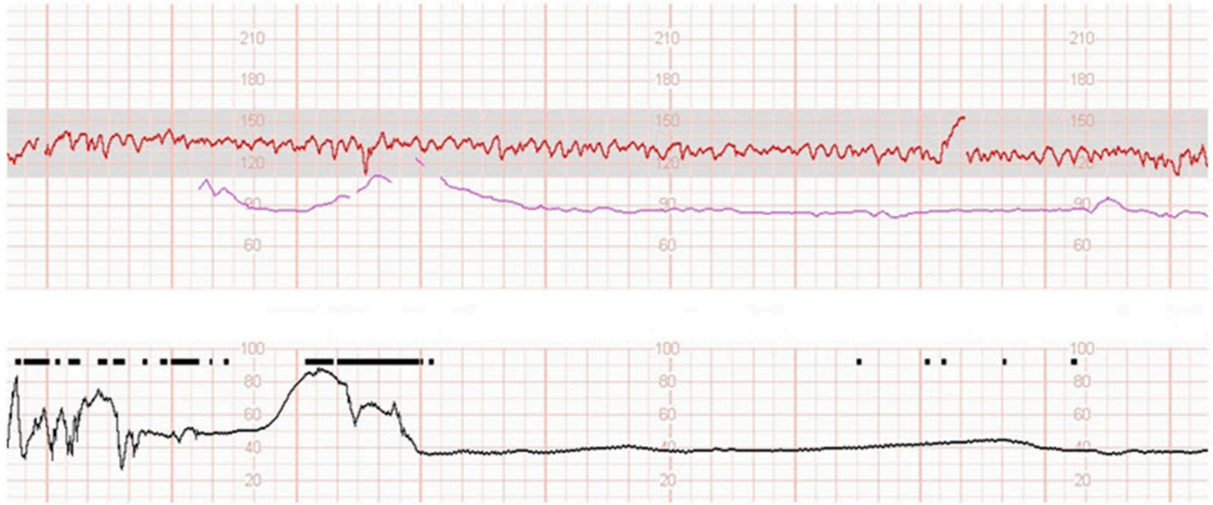

Figure 2. Electronic fetal monitoring strip 2.

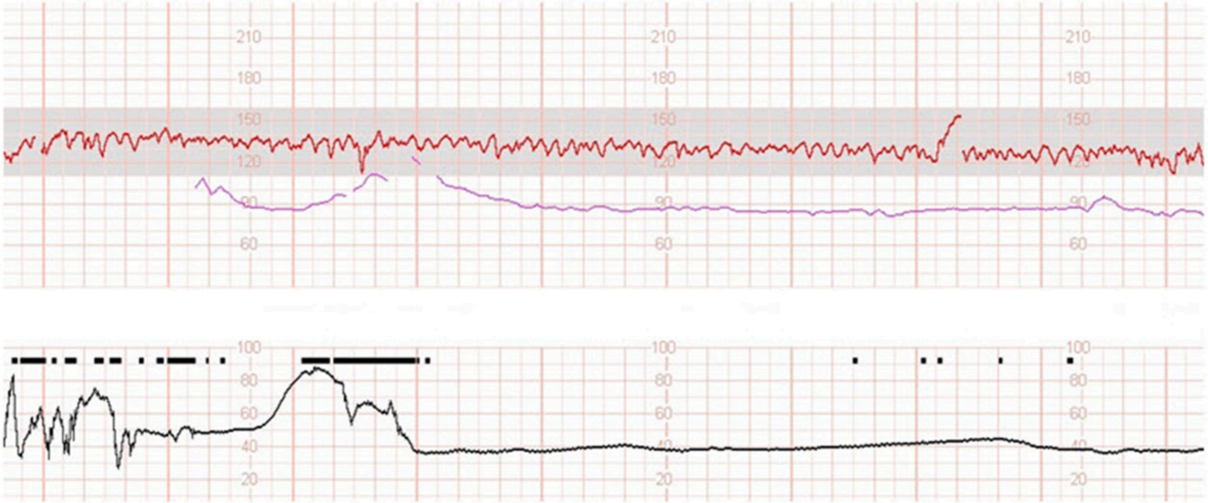

Figure 2. Electronic fetal monitoring strip 2.

Findings from EFM strip 2 are as follows:

- Variability: Moderate
- Baseline rate: 125 beats/min
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: Irregular, intermittent
- Interpretation: Nonreactive, but no signs of fetal acidemia
- Differential diagnosis: Normal FHR tracing, indeterminate fetal heart tracing, fetal acidemia unlikely
- Action: Continue induction of labor with misoprostol

At the time of reevaluation for her third dose of misoprostol (day 2, 6:50 am), the patient had uncomfortable contractions with the external monitor findings shown in Fig 3, consistent with tachysystole. Misoprostol was deferred.

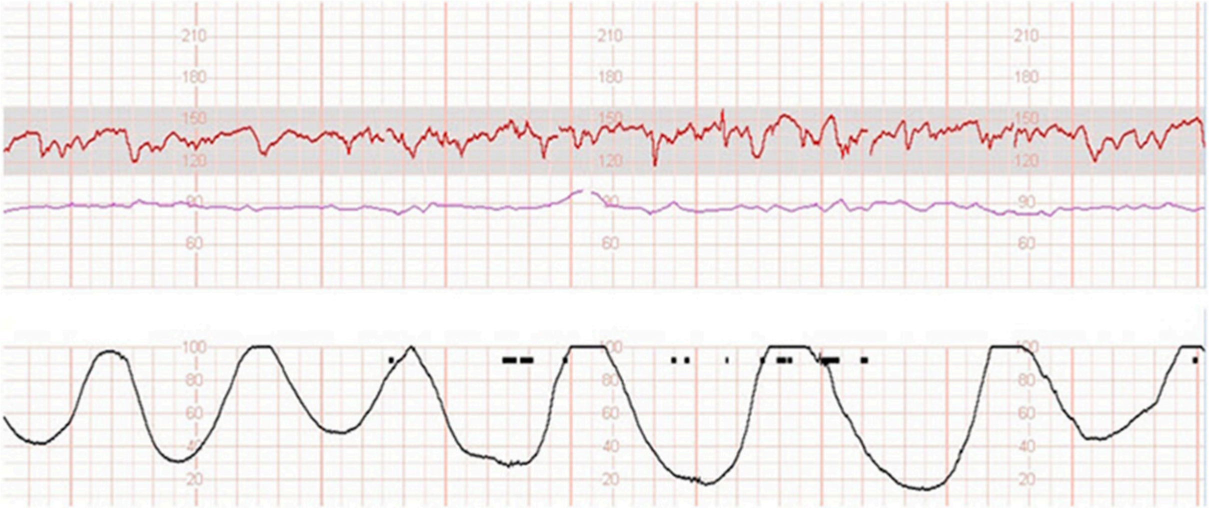

Figure 3. Electronic fetal monitoring strip 3.

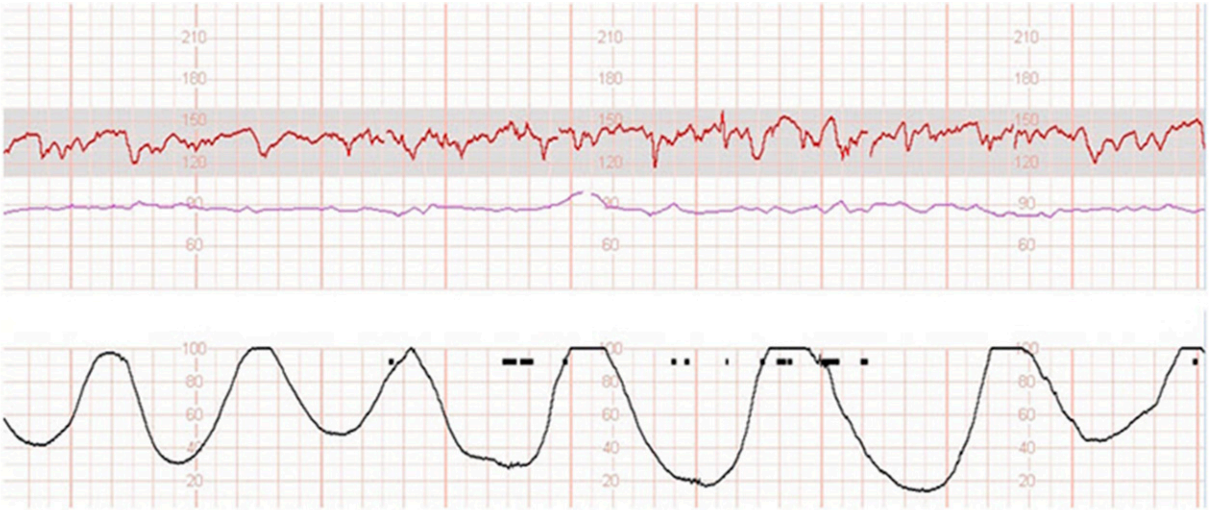

Figure 3. Electronic fetal monitoring strip 3.

Findings from EFM strip 3 are as follows:

- Variability: Moderate
- Baseline rate: 130 beats/min
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: Every 1 to 2 minutes (>5 over a 10-minute period)
- Interpretation: Tachysystole, category 1 fetal heart tracing, negative contraction stress test
- Differential diagnosis: Normal FHR tracing, tachysystole, no evidence of fetal acidemia
- Action: Continuous fetal monitoring, defer continuation of induction of labor with misoprostol in the setting of tachysystole

Her contractions abated after oral and intravenous hydration, and she became much more comfortable. At that time, her FHR tracing was as shown in Fig 4, and a third dose of vaginal misoprostol was placed for an examination of the posterior cervix (day 2, 8:45 am).

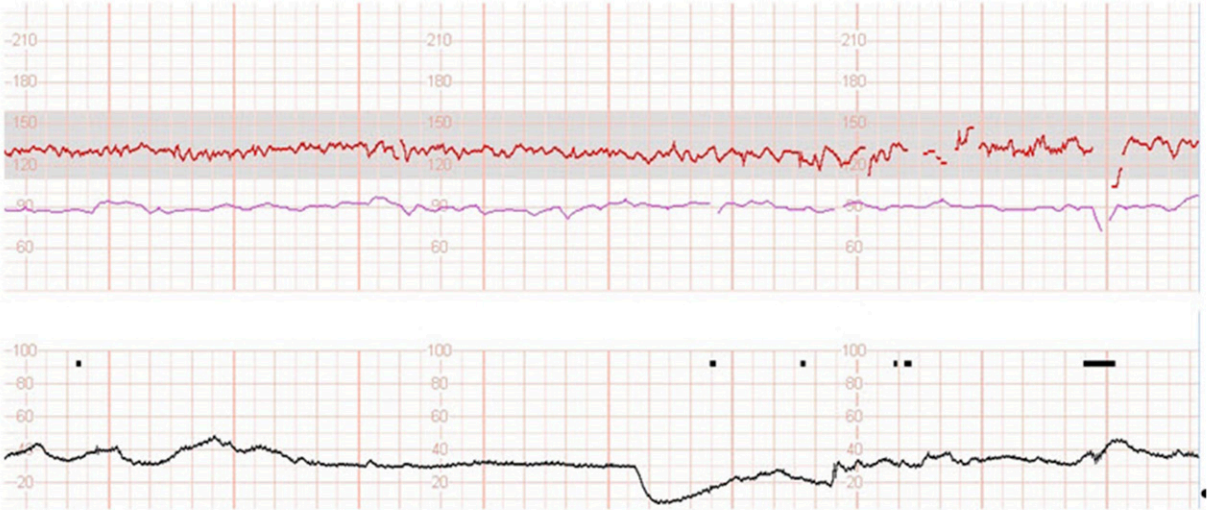

Figure 4. Electronic fetal monitoring strip 4.

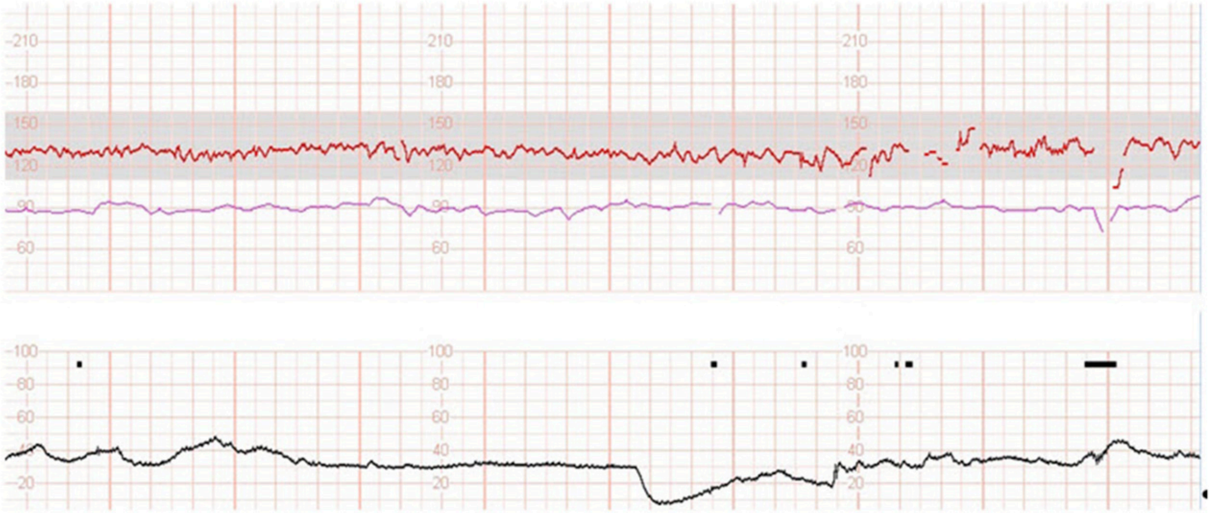

Figure 4. Electronic fetal monitoring strip 4.

Findings from EFM strip 4 are as follows:

- Variability: Moderate
- Baseline rate: 125 beats/min
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: Rare, irregular
- Interpretation: Reactive nonstress test
- Differential diagnosis: Normal FHR tracing
- Action: Continue induction of labor with misoprostol

She was reevaluated for her fourth dose of vaginal misoprostol, which was placed (day 2, 2:54 pm) after reviewing the strip shown in Fig 5. Her cervix remained posterior.

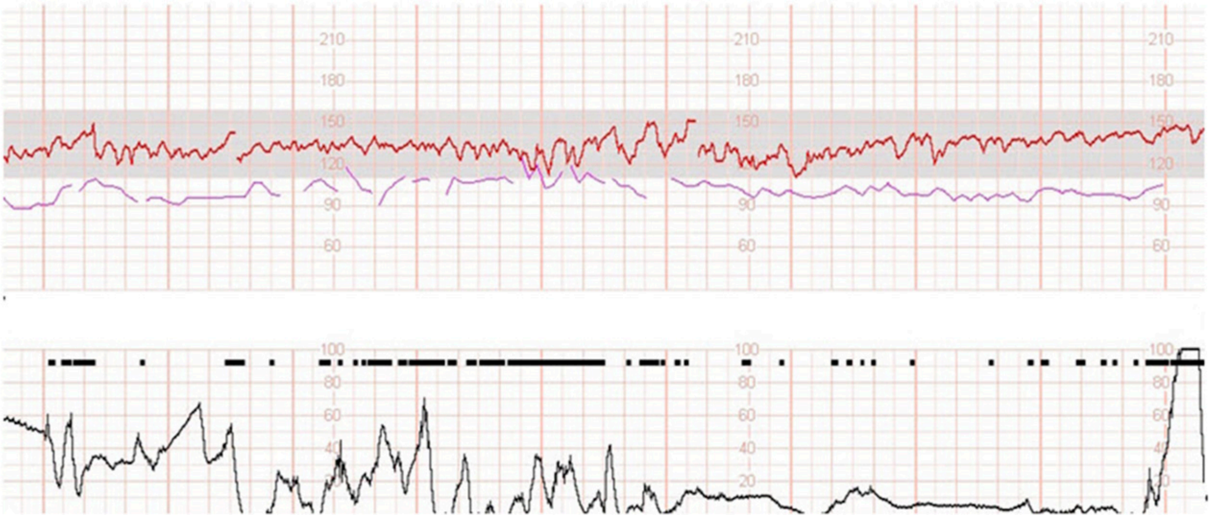

Figure 5. Electronic fetal monitoring strip 5.

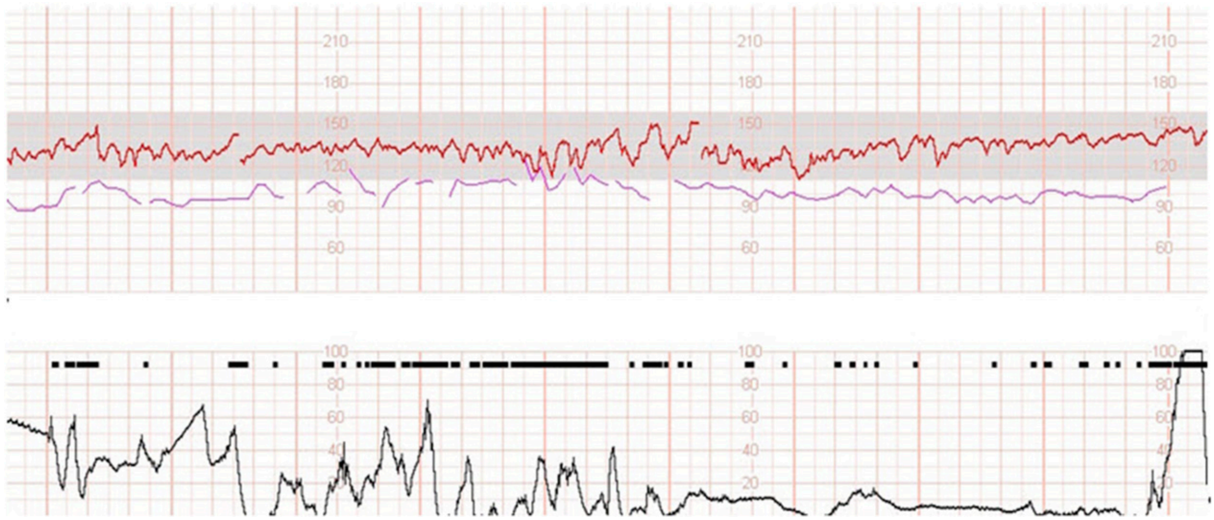

Figure 5. Electronic fetal monitoring strip 5.

Findings from EFM strip 5 are as follows:

- Variability: Moderate
- Baseline rate: 130 beats/min
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: Intermittent, irregular
- Interpretation: Reactive nonstress test
- Differential diagnosis: Normal FHR tracing, no evidence of fetal acidemia
- Action: Continue induction of labor with misoprostol

Two hours later, the patient had spontaneous rupture of membranes notable for meconium-stained fluid (day 2, 4:45 pm). She was given oxytocin (day 2, 8:30 pm) to continue induction. After receiving oxytocin for 4 hours (day 3, 12:24 am), there were concerns about the patient's FHR tracing, as shown in Fig 6. Oxytocin was discontinued.

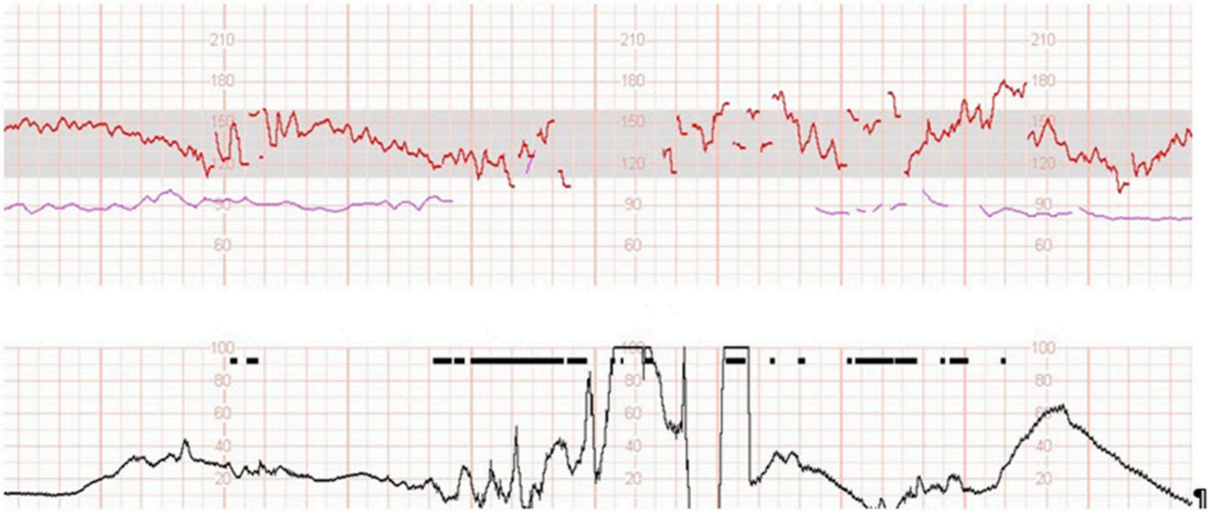

Figure 6. Electronic fetal monitoring strip 6.

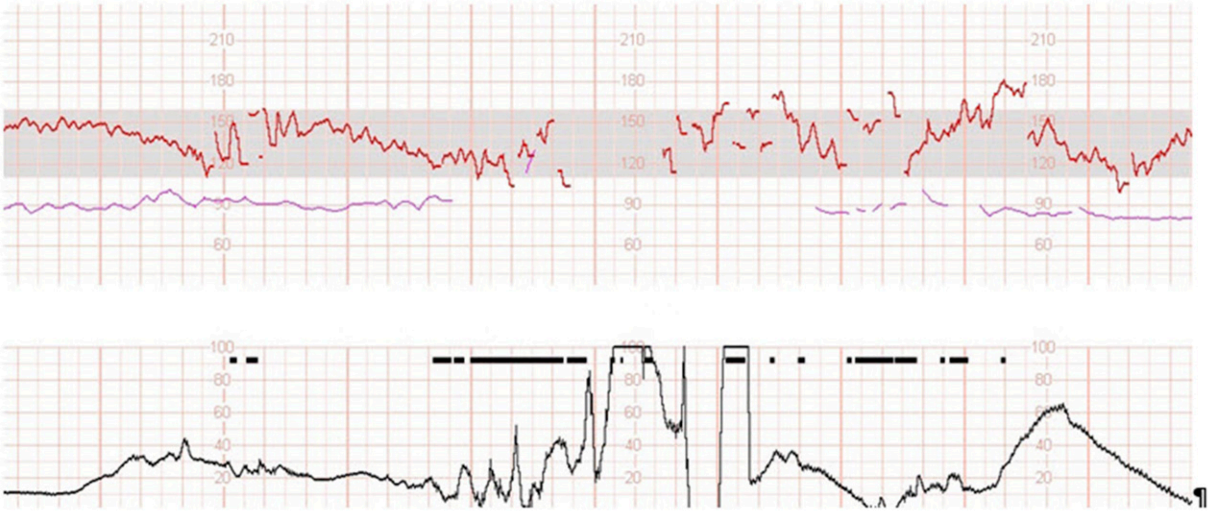

Figure 6. Electronic fetal monitoring strip 6.

Findings from EFM strip 6 are as follows:

- Variability: Moderate
- Baseline rate: 150 beats/min
- Episodic pattern: None
- Periodic pattern: Yes; repetitive late decelerations
- Uterine contractions: Every 4 minutes
- Interpretation: Category II fetal heart tracing (indeterminate)
- Differential diagnosis: Possible fetal acidemia caused by uteroplacental insufficiency
- Action: Discontinue oxytocin

Forty-five minutes later, the fetal heart tracing changed (Fig 7), and oxytocin was restarted (day 3, 1:15 am).

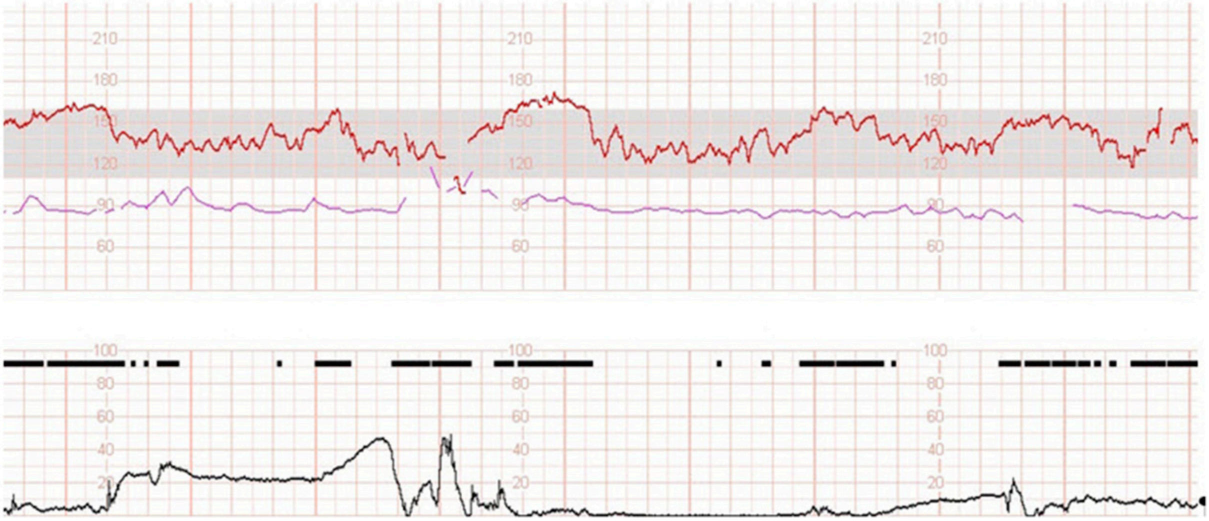

Figure 7. Electronic fetal monitoring strip 7.

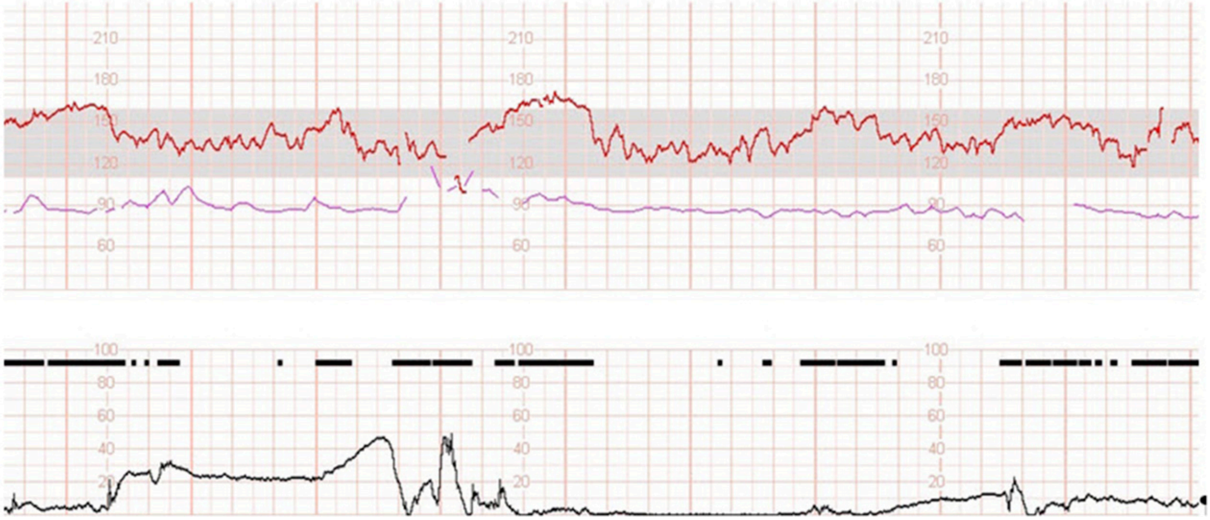

Figure 7. Electronic fetal monitoring strip 7.

Findings from EFM strip 7 are as follows:

- Variability: Moderate
- Baseline rate: 125 beats/min
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: Intermittent, rare
- Interpretation: Category I
- Differential diagnosis: Normal FHR tracing, no evidence of fetal acidemia
- Action: Restart oxytocin for induction of labor

Patient was given hydromorphone for comfort (day 3, 4 am). Her cervix was reexamined (day 3, 5 am) and was found to be 0 to 1 cm dilated, 50% effaced, and high. Shortly thereafter (day 3, 7:30 am), the medical team was called to evaluate the FHR tracing shown in Fig 8.

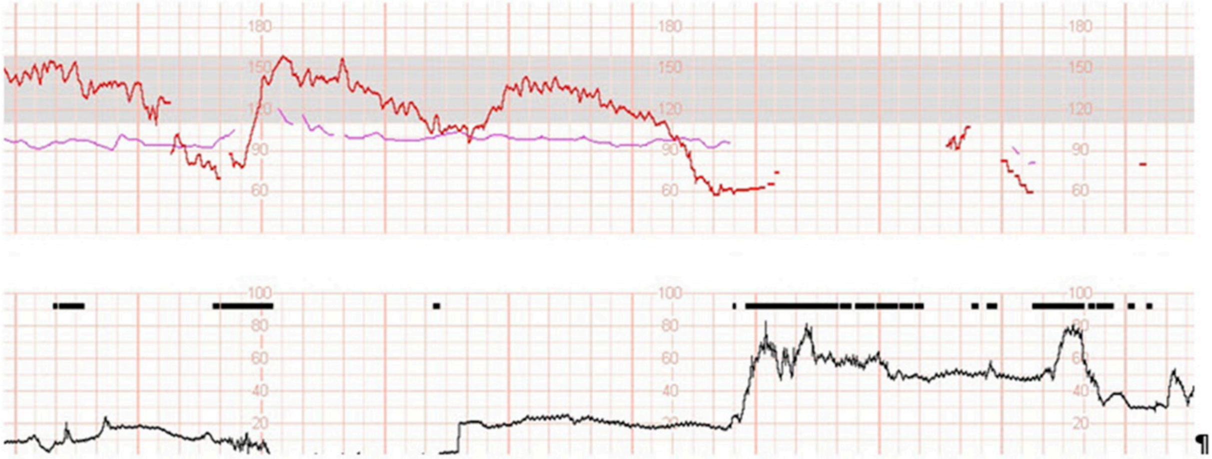

Figure 8. Electronic fetal monitoring strip 8.

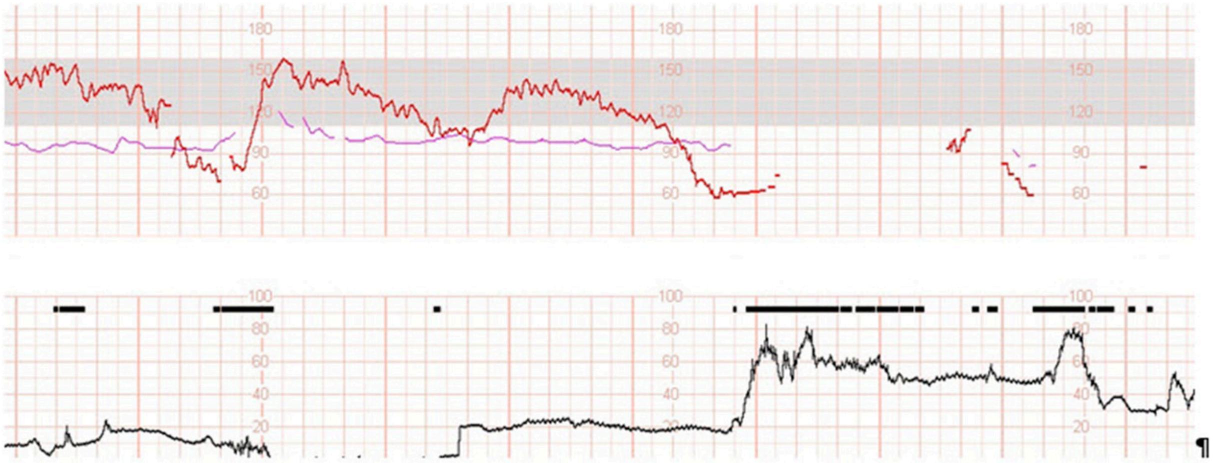

Figure 8. Electronic fetal monitoring strip 8.

Findings from EFM strip 8 are as follows:

- Variability: Moderate
- Baseline rate: 150 beats/min
- Episodic pattern: Yes, variable decelerations
- Periodic pattern: None
- Uterine contractions: Irregular
- Interpretation: Category II
- Differential diagnosis: Possible fetal acidemia caused by cord compression, uteroplacental insufficiency
- Action: Discontinue oxytocin

The FHR deceleration ceased with repositioning and with discontinuation of oxytocin. At that time, the patient's cervical examination finding was unchanged from before.

Two hours later, the team was again asked to evaluate the patient's FHR tracing (Fig 9).

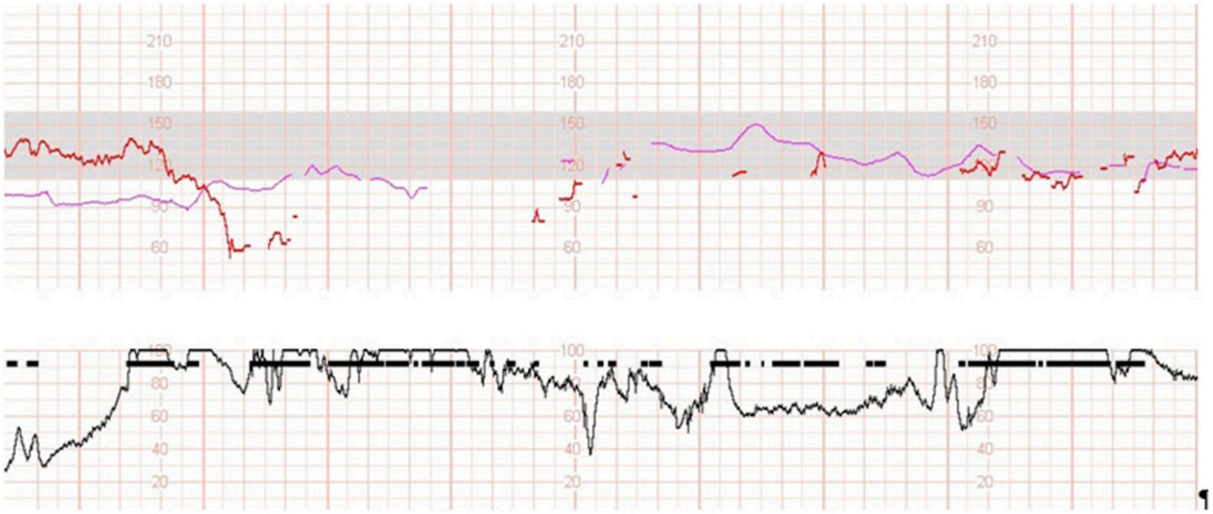

Figure 9. Electronic fetal monitoring strip 9.

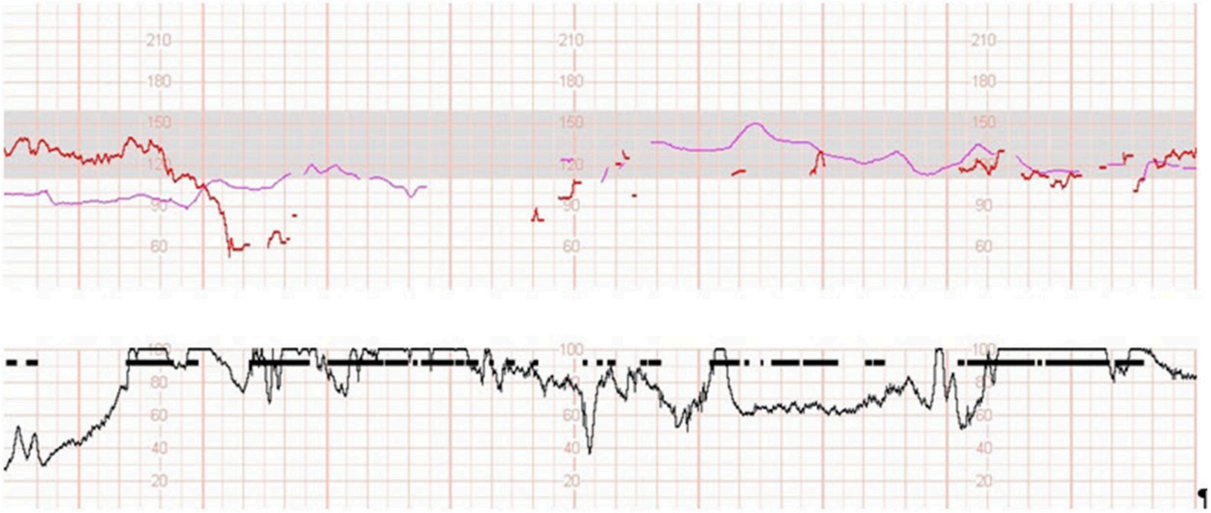

Figure 9. Electronic fetal monitoring strip 9.

Findings from EFM strip 9 are as follows:

- Variability: Unable to assess, given discontinuous strip
- Baseline rate: Unable to assess, given discontinuous strip
- Episodic pattern: Unable to assess, given discontinuous strip
- Periodic pattern: Yes, prolonged deceleration associated with tetanic contraction
- Uterine contractions: Irregular
- Interpretation: Category II
- Differential diagnosis: Poor fidelity of fetal heart tracing, prolonged deceleration associated with tachysystole
- Action: Terbutaline administered; cesarean delivery recommended

Patient's cervical examination finding was unchanged (0–1 cm dilated, 50% effaced, and high). Terbutaline (0.25 mg) was administered in the setting of tetanic contraction, with subsequent recovery of the FHR. However, at that time, the decision was made to proceed to the operating room for a cesarean delivery because of the persistent category II FHR tracing not amenable to intrauterine resuscitation.

Outcome

A vigorous male infant, weighing 3,620 g, with Apgar scores of 8 and 9 (at 1 minute and 5 minutes, respectively) was born via uncomplicated primary low transverse cesarean delivery at a gestational age of 41 4/7 weeks. Estimated blood loss was 700 mL. The infant had an uncomplicated neonatal course and was discharged from the hospital on day 4 after birth in stable condition.

DISCUSSION

Studies have estimated the prevalence of post-term pregnancies to be about 5% to 10%. (1)(2) The causes of late-term (41 0/7 weeks to 41 6/7 weeks) and post-term pregnancies (at >42 0/7 weeks) is unknown, but risk factors include prior post-term pregnancy, nulliparity, male fetus, advanced maternal age, and maternal obesity. (2)(3)

Late-term and post-term pregnancies are at increased risk for perinatal morbidity and mortality. Specifically, studies have shown that post-term pregnancies are associated with increased risks for neonatal convulsions, meconium aspiration syndrome, and a 5-minute Apgar score of less than 4. Post-term deliveries (at >42 weeks) have also been associated with an increase in NICU admissions. Late-term and post-term pregnancies also carry a higher (2-fold) risk of harboring a macrosomic fetus, which has been shown, in post-term pregnancies, to increase the risk of an operative vaginal delivery, cesarean delivery, and shoulder dystocia. (3)

Studies have shown that despite a low absolute risk of stillbirth in post-term pregnancies, the risk increases with each week that the pregnancy continues beyond the estimated due date. (3)

In addition to fetal risks associated with late-term and post-term pregnancies, there are also maternal risks such as severe perineal laceration, infection, postpartum hemorrhage, and cesarean delivery, all of which have been shown to be increased in women with late-term and post-term pregnancies. (3)

Therefore, induction of labor has become common management for pregnancies that continue past a patient's estimated due date. However, expectant management until the post-term period is considered appropriate in the absence of other factors complicating the pregnancy. (3) Antepartum surveillance (typically initiated at or beyond 41 0/7 weeks gestation) can occur while awaiting spontaneous labor. (1)(3) This surveillance is often in the form of a biophysical profile, which evaluates fetal movement, tone, breathing, and amniotic fluid levels as a proxy for fetal well-being. Taking into consideration all evidence available, the American Congress of Obstetricians and Gynecologists states that induction of labor "can be considered" between 41 0/7 and 42 0/7 weeks' gestation and is "recommended" after 42 0/7 weeks given perinatal morbidity and mortality associated with post-term pregnancies. (2)(3) In the absence of any fetal or maternal factors mandating cesarean delivery, vaginal delivery should be anticipated. (4) In fact, studies that have compared mode of delivery in induction of labor for post-term pregnancies versus awaiting spontaneous labor have shown either no difference or a lower risk of cesarean delivery after the induction of labor. (2) However, it has been shown that nulliparous women with unfavorable cervixes who are undergoing induction of labor do carry a 2- to 3-fold elevated risk of having a cesarean delivery. (4)(5) It has also been established that the labor curve for patients undergoing induction varies compared with women who go into spontaneous labor. More specifically, the latent phase of labor in the former population may be longer (12–18 hours) than in the latter. Being mindful of these expectations for a patient's labor curve may decrease the risk of cesarean delivery in the setting of an induction that is deemed to have "failed." (4)(5)

Aside from an arrest of labor or a failed induction, unscheduled cesarean delivery may occur in the setting of a persistent category II or III FHR. Continuous fetal heart monitoring has traditionally been used as a proxy for fetal well-being. During labor, categories are assigned to heart rate patterns based on features such as heart rate, variability, and presence of decelerations. Category I fetal heart tracings strongly suggest that the fetus is adequately oxygenated and not acidemic, whereas category III fetal heart tracings (absent variability with either bradycardia or recurrent late or sinusoidal pattern) indicate increased risk that a fetus is acidemic and warrants expedited (immediate) delivery. Category II fetal heart tracings have been deemed intermediate and represent a wide spectrum of patterns; data have shown that as long as variability and/or accelerations are preserved, this category of heart tracings are highly predictive of normal fetal acid-base status. Therefore, it is often appropriate in the clinical setting to continue intrauterine resuscitation with close monitoring as long as progression is occurring toward delivery. If a fetus demonstrates a persistent category II fetal heart tracing that is not responsive to intrauterine resuscitation or is remote from delivery, expedited delivery (operative vaginal or cesarean) may be warranted. (6)

In summary, late-term or post-term induction of labor is intended to improve fetal outcomes and most often results in a spontaneous vaginal delivery; however, certain risk factors such as nulliparity or an unfavorable cervix may be associated with an increased risk for cesarean delivery. (1)(2)(3)(4)(5) As with any labor course, cesarean delivery is also warranted as an intervention for a persistent category II or III FHR tracing that does not respond to intrauterine resuscitation or is remote from delivery. (6)

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the definition, risks to the fetus and/or newborn infant, and management of post-term pregnancy.

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Female Newborn with Extreme Hyperextension of Right Knee

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THE CASE

A term female infant is seen with extreme hyperextension of the right knee after birth.

PRENATAL, BIRTH, AND FAMILY HISTORIES

- Born to a 21-year-old white primigravida woman.
- Maternal history of autoimmune thyroiditis with normal thyroid function during pregnancy.
- No history of musculoskeletal anomalies or neuromuscular disorders.
- Nonconsanguineous spontaneous conception; normal fetal survey with normal amniotic fluid; normal maternal perception of fetal movements.
- Maternal group B *Streptococcus* colonization and adequate intrapartum penicillin prophylaxis. Remaining prenatal laboratory screenings negative.
- Female infant in cephalic presentation born at 39 weeks' gestation by spontaneous vaginal delivery.
- Apgar score: 9 and 10 at 1 and 5 minutes, respectively.
- Birthweight: 3,060 g (50th percentile); length: 48 cm (50th percentile); head circumference: 32.5 cm (15th percentile).

PRESENTATION

The female infant presents at birth with marked asymmetry in posture with hyperextended right knee resistant to flexion (Figs 1-4).

PROGRESSION

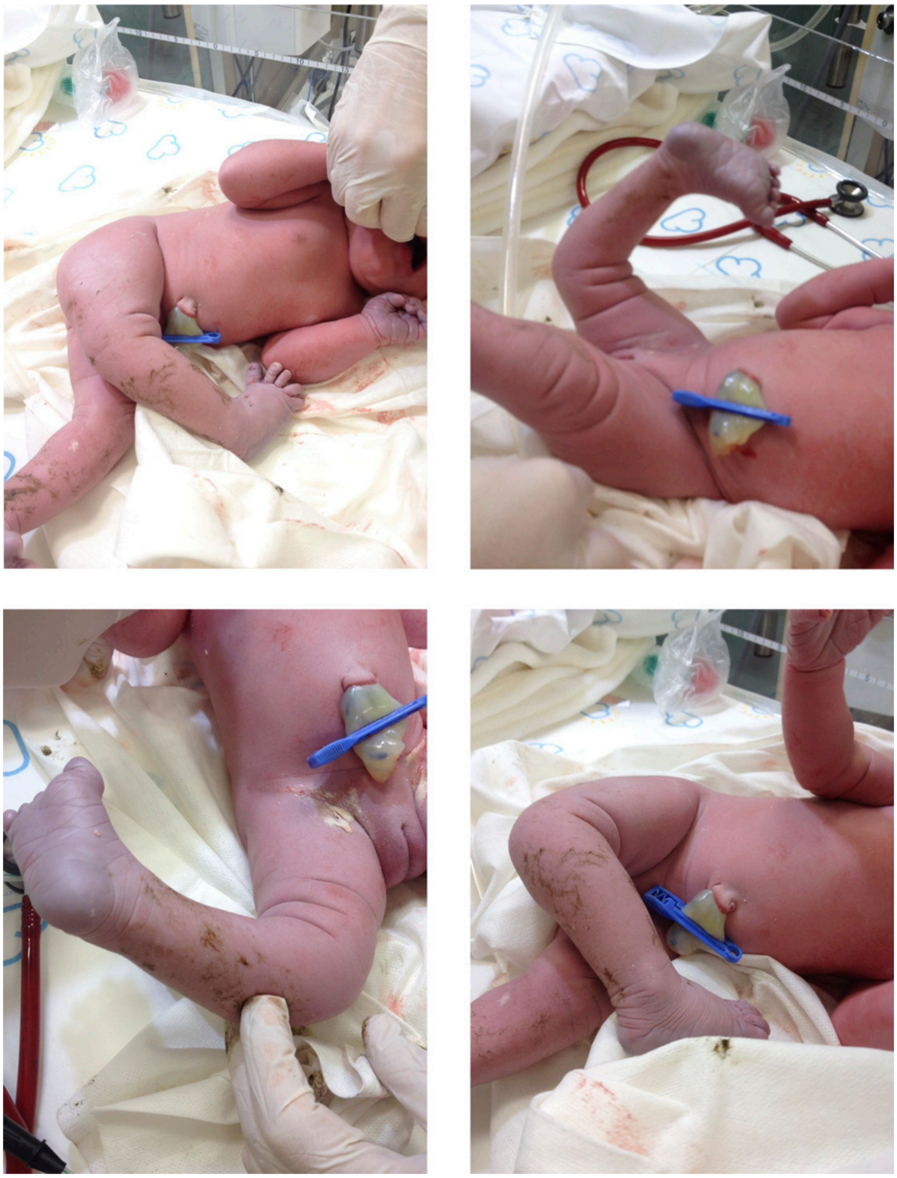
Vital Signs

- Heart rate: 149 beats/min
- Respiratory rate: 55 breaths/min
- Blood pressure: 66/41 mm Hg (mean 50 mm Hg)
- Oxygen saturation: 96% (in room air)
- Temperature: 97.5°F (36.4°C)

Physical Examination

- Head: Normocephalic; normal facial features; normal, open, flat fontanelles; symmetric facies; patent nares; intact palate; no neck mass or crepitus
- Oral cavity: Pink mucosae, intact palate, no lymphadenopathy, and normal sucking and rooting reflex

AUTHOR DISCLOSURE Drs Falcão, Almeida, Carvalho, Campos, and Neiva-Araújo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figures 1-4. Extreme hyperextension of right knee at birth.

- Lungs: Clear, equal breath sounds; no respiratory distress
- Cardiovascular: Normal S1, S2; regular rate and rhythm; no murmurs or gallops
- Abdomen: Soft, no abdominal distention; normal umbilical cord, no mass or organomegaly, normal bowel sounds
- Genitourinary: Normal term female genitalia; patent anus
- Skin: No icterus, birthmarks, or other rashes
- Musculoskeletal: Instability of right knee in all directions; hyperextension of 90 degrees with no active flexion and a passive range flexion of 5 to 10 degrees; presence of 3 transverse anterior skin grooves; normal left leg and both arms; normal Ortolani and Barlow signs; no evidence of clubfoot; normal appearance of spine.
- Neurologic: Symmetric Moro reflex, normal strength and tone

Radiographic and Ultrasonographic Studies

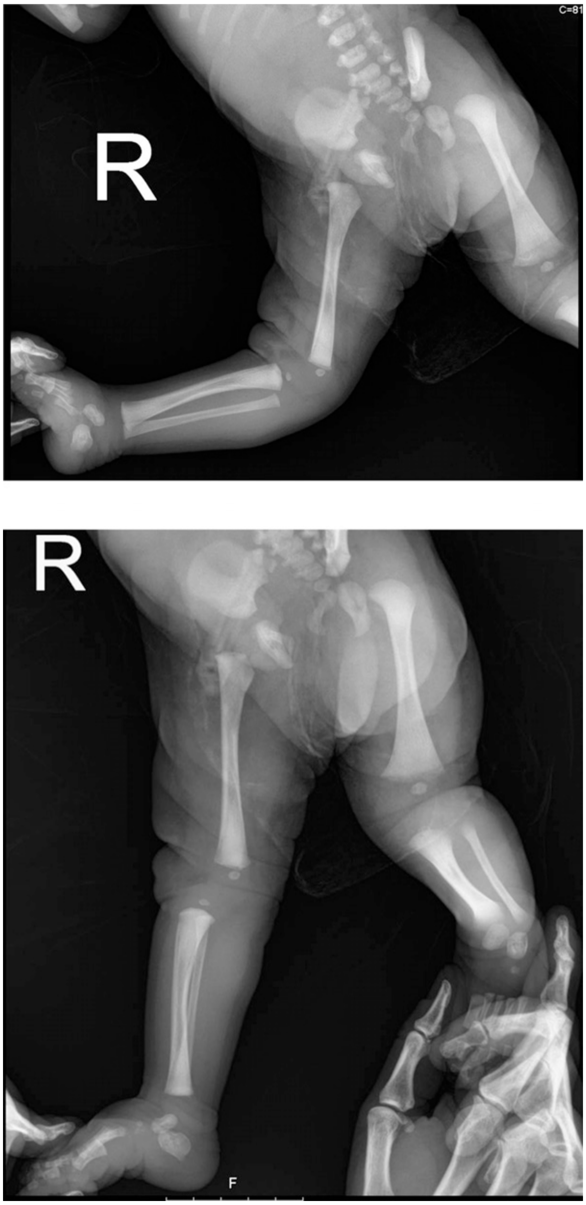
- Radiography of the right leg revealing subluxation of the knee joint (Figs 5 and 6)
- Hip ultrasonography at age 2 months without coxofemoral luxation

DIFFERENTIAL DIAGNOSIS

- Simple genu recurvatum
- Congenital dislocation of the knee
- Larsen syndrome
- Arthrogryposis multiplex congenita

ACTUAL DIAGNOSIS

Congenital dislocation of the knee with subluxation, grade 2.



Figures 5 and 6. Lateral view in hyperextension and neutral position of the right knee showing pathologic joint.

The orthopedics team evaluated the newborn 1 hour after birth. Neurovascular pathology was excluded. The orthopedists performed progressive reduction by gentle manipulation and cast immobilization, ensuring stability of the affected joint (Fig 7). Follow-up at 1 week showed clinical improvement, with confirmation of stability of the right knee. Previous pathologic posture of the right knee was corrected at 2 weeks and no deformity was noticed (Fig 8).

WHAT THE EXPERTS SAY

Congenital dislocation of the knee (CDK) is a rare congenital anomaly of the musculoskeletal system that was first described in the 19th century. It occurs in 1 in 100,000 live births and includes a range of deformities from subluxation to complete dislocation. (1)(2)(3) Most cases of CDK are sporadic, but some case reports have described familial occurrence. (3) This entity can be isolated or associated with other musculoskeletal anomalies such as development dysplasia of the hip and clubfoot. It can also be associated with a syndrome such as Larsen syndrome or arthrogryposis multiplex congenita. (4)(5) There are many hypotheses about the

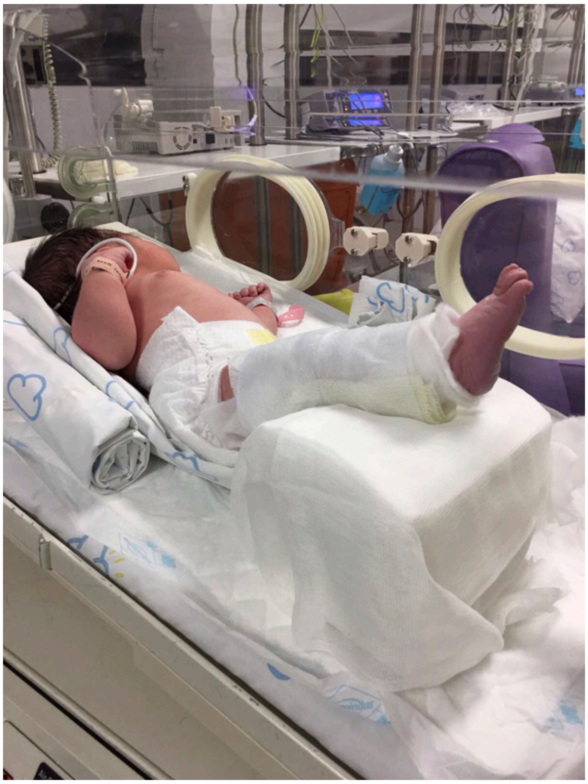


Figure 7. Reduction of the dislocated knee and immobilization with a splint.

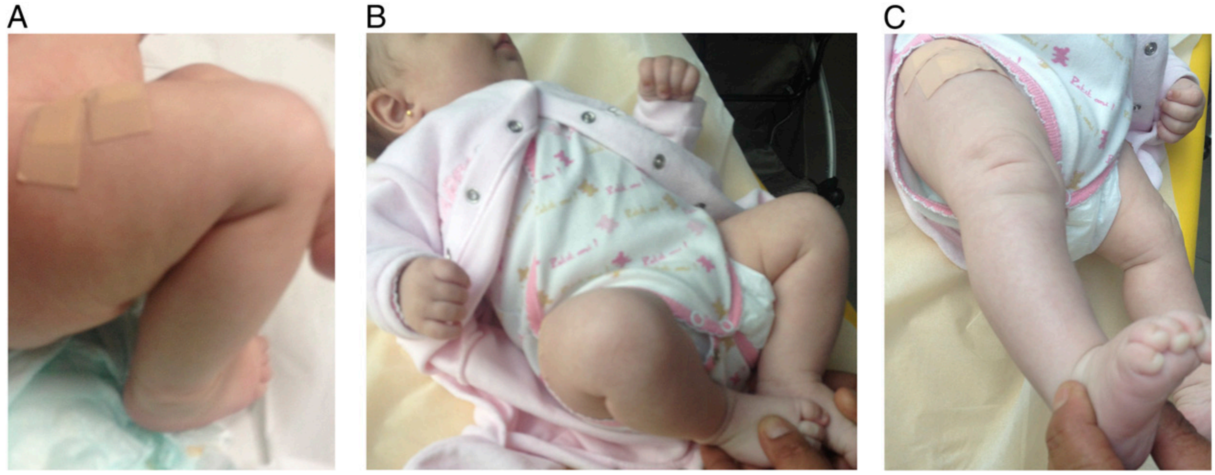


Figure 8. Follow-up at age 2 months showed normal posture. A, active flexion; B, passive flexion; C, extension of the knee.

etiology of CDK, including intrinsic and extrinsic causes. The intrinsic causes include genetic abnormalities, while the extrinsic causes are attributable to mechanical factors, such as oligohydramnios, decreased intrauterine space, malposition of the fetus, fibrotic contracture of the quadriceps, and traumatic dislocation during birth. (3) Diagnosis is made after birth based on clinical findings of a pathologic position of the knee with radiographic confirmation. (4)

This deformity can be classified into 3 subgroups:

- Grade I, genu recurvatum: This is the most common type. It is not a true dislocation but rather, described as a congenital hyperextension. In this case, nearly 15 to 20 degrees of hyperextension and a maximum passive flexion of 90 degrees can be achieved.
- Grade II: This includes congenital subluxation with joint incongruence. Passive flexion of the knee is impossible and 25 to 40 degrees of hyperextension can be achieved.
- Grade III: This includes cases with no contact between the joint surfaces of the tibia and femur with proximal tibial epiphysis located anterior to the femoral condyles. (6)

Mehrafshan and colleagues recently suggested another approach to classification based on reduction and stability. This approach distinguishes CDK into 3 types: I, reducible; II, recalcitrant; and III, irreducible. As well as being of prognostic value, it can serve to guide management. The authors report that clinical signs such as anterior grooves and range of movement are important prognostic tools. They found that the greater the number of transverse anterior skin grooves, the more recent is the intrauterine origin of dislocation; in contrast, the absence of grooves indicates a long-standing dislocation. Flexion of the joint is more impaired in more severe cases. (4)

If affected patients are untreated, they can develop stiff and unstable knees. (5) Early nonoperative reduction is the current recommended approach for infants with CDK. (3) Management should be initiated soon after birth using gentle manipulation and serial casting in progressive flexion until right-angle knee flexion is achieved. (7) When this conservative treatment is started within 24 hours after birth, outcomes are good, regardless of the type and severity of associated anomalies, emphasizing the important role of early referral. (1)

The prognosis for infants with CDK depends on early treatment and whether there are other congenital anomalies. In general, results are worse if the dislocation is irreducible; when there is an associated general syndrome; and when knee flexion is less than 50 degrees in the absence of anterior skin grooves. (8) Furthermore, Cheng and Ko found increasing difficulty in reducing CDK when the procedure was attempted later after birth. Indeed, reduction was easier in patients treated less than 8 hours after birth. (3) Neonatologists and pediatricians can play a key role in the management and prognosis of CKD by immediate recognition of this condition and quick referral to orthopedics.

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Understanding the Limitations of Feral Cardiac Imaging: 1. B; 2. D; 3. A; 4. C; 5. E.

Universal Screening for Perinatal Depression: 1. B; 2. A; 3. D; 4. A; 5. D.

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Answer Key appears on page e268

Human Milk Banking: An Indian Experience

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Education Gaps

1. There is a scarcity of systematic data on human milk banking practices in India.
2. The role of policy and technical leaders in promoting human milk banking as part of an integrated approach in optimizing neonatal health needs to be understood.

Abstract

As part of integrated newborn care, human milk banks can reduce death and illness as well as lower health-care costs for infants born prematurely, especially with birthweights less than 1,500 g, and for infants born in resource-limited settings without access to their mother's milk. Promotion of human milk banks is of special significance in India which has the highest burden of such infants. About 50 milk banks are insufficient to meet the needs of vulnerable infants. The government of India has acknowledged the role that human milk banking can play in reducing neonatal mortality and morbidity, and launched the "National Guidelines on Lactation Management Centers in Public Health Facilities" in 2017 with a vision to make breast milk universally available for all infants. The government is now working on an implementation strategy to scale up the lactation management center model (promotion of breastfeeding, kangaroo mother care, and donor human milk) for all newborn care units and delivery centers in the country. However, for effective expansion, it will be important to ensure improved government ownership, mandate availability of standard operating procedures at all facilities, stringent systems of quality control, standardized accreditation, and a robust monitoring system. Local evidence on the effectiveness of the comprehensive lactation management center (CLMC) model and knowledge, practices, and perceptions of human milk banking are limited. There is a need for rigorous implementation, process research, and technology innovation, along with a robust regulatory framework to prevent commercialization. In addition, attitude changes of mothers, maternal influencers, and health-care providers are all essential to successfully expand the CLMC model.

AUTHOR DISCLOSURE Drs Nangia and Sabharwal and Ms Sachdeva have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CLMC	Comprehensive Lactation Management Center
LMU	lactation management unit
LSU	lactation support unit
MAA	mother's absolute affection
MOM	mother's own milk
MBFI+	Mother Baby Friendly Initiative *Plus*
NMR	neonatal mortality rate

Objectives After completing this article, readers should be able to:

1. Describe how prioritizing an integrated approach in human milk banking can save lives in India.
2. Recognize the salient features of the national guidelines on human milk banking along with the human milk banking environment in India.
3. Outline key initiatives to be addressed for effective scaling up of human milk banking in India.

THE POWER OF HUMAN MILK

Breastfeeding is the most natural, inexpensive, environment-friendly, and easily accessible method to provide all children, rich or poor, with the healthiest start to life and ensures that all children survive and thrive. Breast milk offers the ideal source of nutrition for the first 6 months after birth, and may remain a part of an infant's diet for the first 2 years of age and beyond. (1) There is evidence that demonstrates the value of breastfeeding for both a mother and her child. *Sushruta*, an ancient Indian surgeon, has beautifully described mother's milk in his *Samhita*, "One just cannot compare even water of seven seas with mother's milk, which is nothing but water ensuring optimum growth, nutrition, and healthy life of hundred years." (2)

However, many infants lack access to their mother's own milk (MOM) because of issues related to the mother's illness or death, abandonment, infant's illness, inability to latch, or delay in milk production. This lack of access to breast milk leaves infants more vulnerable to disease, poor health, or death, especially when they are born preterm, have low birthweight, or are severely malnourished. (3)(4)(5) In such a scenario, the World Health Organization, (6) American Academy of Pediatrics, (7) the Committee on Nutrition of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, (8) and other policy groups recommend donor human milk, made available through human milk banks, as the next best feeding option when MOM is unavailable. A human milk bank screens and recruits breast milk donors; collects, processes, and screens donated milk; and distributes the milk to infants in need.

As part of integrated newborn care, human milk banks reduce death and illness as well as lower health-care costs. Data exist, which support the health benefits of donor human milk, especially for infants born prematurely, with birthweight less than 1,500 g, (9) and for infants born in resource-limited settings where a non-breastfed child's risk of death is 6 times that of a breastfed child. (10) A myriad studies demonstrate the positive effect of donor human milk on vulnerable infants as compared with formula, such as reduced risk of sepsis and necrotizing enterocolitis, greater feeding tolerance, reduced length of stay in NICUs, and substantial cost savings for resource-strapped public health systems (Table 1). (8)(11)(12)(13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)(26)

A recent study found that if all premature infants born in the United Kingdom in 2013 were provided with mother's milk in the NICU, the total lifetime cost savings to the National Health System would be an estimated $46.7 million (£30.1 million in the first year) as a result of improved health outcomes. The total lifetime quality-adjusted life-year gain was calculated to be 10,594 years. There would be 238 fewer deaths caused by neonatal infections and sudden infant death syndrome, leading to a savings of approximately £153.4 million in lifetime productivity. (27)

Providing donor human milk to vulnerable neonates without access to MOM not only saves lives but also enhances awareness about breastfeeding and improves breastfeeding rates. This increase in breastfeeding rates is important because it has the potential to prevent 820,000 "under-5" deaths (ie, death before age 5 years), of which 87% are infants younger than 6 months of age. (28) Improving breastfeeding rates worldwide is a fundamental driver to achieve Sustainable Development Goals by 2030.

HUMAN MILK BANKING: A CENTURY-OLD PRACTICE

Saving infants with the use of donor human milk through human milk banks is a century-old practice. Countries in North America and Europe established human milk banks in the early 20th century. The United Kingdom established its first human milk bank in the 1930s, and Brazil in the 1940s. Today, more than 600 milk banks have been established in more than 50 countries. Human milk banks have been extremely successful in Brazil, its network being the largest in the world with 213 milk banks and 199 collection

TABLE 1. **Studies Demonstrating the Impact of Donor Human Milk on Vulnerable Infants**

Sepsis	• Donor human milk reduced the risk of late-onset sepsis in vulnerable, low-birthweight infants by 19% in the first 28 days. (11) • Donor human milk has a greater protective effect compared with formula. (12)
Necrotizing enterocolitis	• Human milk feeding, whether mother's own milk or donor human milk reduces necrotizing enterocolitis by as much as 79% when formula is avoided. (13) • Four systematic reviews across study designs and countries found that donor human milk protects preterm infants against necrotizing enterocolitis more than formula. (8)(14)(15)(16)
Retinopathy of prematurity	• Human milk feeding in the NICU is associated with lower rates of severe retinopathy of prematurity. (17,18)
Feeding tolerance	• Preterm infants fed unfortified donor human milk had greater feeding tolerance, fewer vomits, less gastric stasis, and reduced diarrhea compared with formula-fed infants. (16)
Reduced length of stay in NICU	• Cost of providing donor human milk to preterm infants is mitigated by a reduced risk of complications and shorter length of stay in NICU. (11)(19) • Fewer hospital readmissions for illness in the year after NICU discharge have been noted. (20)
Cost saving	• The percentage of infants who are exclusively breastfed at discharge is about 13% higher in NICUs with a human milk bank. (21) • A study reported saving ~US $8,167 per infant using donor human milk through shortened length of stay and reduced cases of necrotizing enterocolitis and sepsis. (19) • Estimated savings to NICU or health care plan for every dollar spent on donor human milk: ~US $11. (22) • In Brazil, the national human milk banking network saves $540 million in health care costs annually. (23)
Neurodevelopmental outcomes and long-term benefits	• Later in childhood and adulthood, preterm infants fed human milk have been shown to have lower rates of metabolic syndrome, (24)(25) increased white matter and brain volume, and significantly greater scores for mental, motor, and behavior ratings. (19)(26)

centers. The Brazilian Network of Human Milk Banking has successfully demonstrated the effectiveness of a government-supported, nationalized, integrated human milk bank program that includes breastfeeding promotion, lactation support, and provision of donor milk, all of which have contributed to achieving a single-digit neonatal and infant mortality rate. Brazil's integrated human milk banking program saves the country an estimated $540 million annually through improved neonatal health outcomes. (29)

PRIORITIZING AN INTEGRATED APPROACH FOR HUMAN MILK BANKING IN INDIA

India faces its own unique challenges. The country is the highest contributor to the global birth cohort, neonatal mortality rate, and birth of vulnerable infants, that is, infants born prematurely and with low birthweight. Of the 27 million infants born in India annually, 30% are born with low birthweight (ie, weighing <2,500 g), and 40% of all low-birthweight infants (estimated at 3.5 million infants), are born preterm (Fig 1). (30) Of the 0.76 million infants who die in the neonatal period, prematurity is the major cause, accounting for 35% of all deaths, followed by infection, accounting for another 33%. (30)

India has made considerable progress over the last 2 decades in the area of maternal and child health through innovative and comprehensive health packages that cover the spectrum of life cycle stages. However, newborns have missed out on the attention. Even though the under-5 mortality rate decreased by 42%, from 74 (in 2005–06) to 43 (in 2015) per 1,000 live births, in the same period, neonatal mortality rate (NMR) decreased from 37 to 25 per 1,000 live births, accounting for a decrease of only 32%. (31)(32) This decline in NMR is laudable but it has to increase to effectively achieve sustainable development goals, which aim to eliminate preventable deaths of children less than 5 years of age, with all countries aiming to decrease the NMR to as low as 12 per 1,000 live births. (33)

About 75% of premature infants can be saved with feasible and cost-effective interventions. These include kangaroo mother care; adequate neonatal resuscitation; prevention, detection, and treatment of neonatal infections; and breastfeeding. (34) Of these, breastfeeding has been identified as the single most powerful intervention, with the potential to prevent 0.16 million under-5 deaths in India. (28) Yet, breastfeeding rates remain low, with only 41.6% of infants being initiated into breastfeeding within 1 hour of birth and 54.9% of infants exclusively breastfed until 6 months of age. (35)

Breastfeeding has a pertinent and important role to play in improving the status of neonatal health in India. This emphasizes the need to universalize access to human milk as an integral component in the country's health-care system, especially in all newborn units that provide care to sick infants. Providing human milk through human milk banks can work only if it is a part of the larger objective of promoting breastfeeding. There is a need to link human milk banking systems with breastfeeding and kangaroo mother care by establishing high-quality systems, sharing global best practices, and facilitating capacity building. An integrated intervention will not only assist in feeding human milk to preterm and low-birthweight infants, but will also increase breastfeeding rates in the country. Previous experience shows that human milk banks thrive in countries where they are protected, promoted, and endorsed as a critical component of breastfeeding and newborn care policies. (29)

Based on its existing toolkit on the establishment of human milk banks, "Strengthening Human Milk Banking: A Global Implementation Framework,"(36) PATH has proposed the "Mother Baby Friendly Initiative *Plus*" (MBFI+) model in which human milk banks collect, process, and store donor human milk while serving as centers that provide lactation and kangaroo mother care support. (29) Because successful breastfeeding often requires support from the family and community, the model also positions human milk banks to work with and engage local communities. These banks promote the significance of breastfeeding and milk donation, build awareness about the value of human milk, and collaborate with employers and other leaders to create an enabling and supportive environment for breastfeeding and milk donation. (36) The MBFI+ model is deliberately intended to be altered by each country to fit its unique needs. Similarly, the model has been adapted to suit India's public health structure (Fig 2).

HUMAN MILK BANKING LANDSCAPE IN INDIA

In India, voluntary donation of human milk in the form of wet nursing has been an integral part of its tradition. Mythological anecdotes tell tales of *Yashoda*, who was a wet nurse (human milk donor) to Lord *Krishna*. In the 18th century, wet nursing was widely practiced for offspring of mothers born into nobility who refused to breastfeed their infants to preserve their beauty and figure. Later, the practice declined because of a fear of transfer of infections and diseases such as syphilis. Much later, the concept of human milk banks was introduced.

In Asia, the first human milk bank was established in 1989 by Dr Armida Fernandez in Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, India. The milk bank was started after realizing the acute need to save sick infants in hospitals. It soon became sustainable as mothers who had delivered at the hospital and donated milk to the milk bank returned for follow-up care. (37) Despite the successful establishment of this bank, other hospitals were not encouraged to take up this venture and this remained the only human milk bank in the country until the year 2005. From 2005 to 2015, only 22 human milk banks were established, but in the past 2 years, this number has more than doubled. There are currently about 50 milk banks in India, which are still inadequate to meet the massive demand for donor human milk (Fig 3). To put this in perspective, the United Kingdom has 770,000 births each year and 16 operational milk banks, whereas India has 27 million births each year and only 50 operational milk banks.

Historically, implementation of effective regulated, country-specific, human milk banks have been slow to develop in India. Initially, human milk banks were concentrated in the western belt of the country because the first human milk bank was established in this region, and the majority of milk banks were modeled on this first one. The development of milk banks has met with several challenges including inadequate collaboration between obstetricians and pediatricians, lack of lactation counselors, and limited awareness. (37) There are also gaps in providing able leadership for sharing best practices and robust procedures. However, the changing landscape has facilitated an expansion in human milk banks in some parts of the country.

INDIA-SPECIFIC STUDIES ON HUMAN MILK BANKING

A recent study conducted to understand current practices, processes, infrastructure, personnel structure, and funding mechanisms in human milk banks with minimum 1 year of functioning (n=16) revealed that standardization of processes as well as data capturing and reporting were urgently needed. (38) Only 25% of the study sites pooled milk under laminar airflow. Sixty-two percent of the facilities used steel containers for milk pasteurization and storage, which is unique to India. Because steel is widely used in homes and laboratories and has good conductivity, it results in faster heating and cooling cycles. This helps preserve milk nutrients better, especially its sensitive immunologic components, because the duration of exposure to extremes of temperature is curtailed. Steel can be easily cleaned and sterilized by exposure to dry heat in a normal oven, therefore, it has been an obvious choice of milk banks in India. Only 50% of milk banks had dedicated full-time technicians. In the remaining milk banks, lactation counselors and other

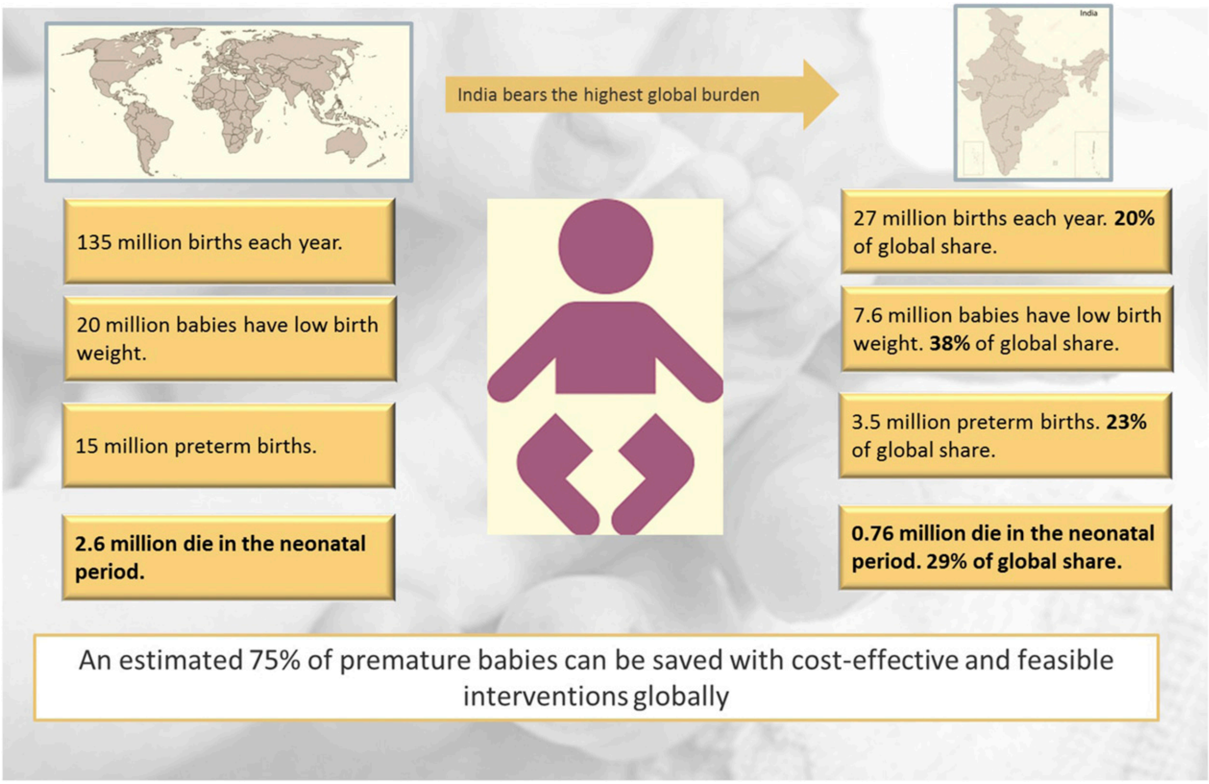
India bears the highest global burden
India
135 million births each year.
20 million babies have low birth weight.
15 million preterm births.
2.6 million die in the neonatal period.
27 million births each year. **20%** of global share.
7.6 million babies have low birth weight. **38%** of global share.
3.5 million preterm births. **23%** of global share.
0.76 million die in the neonatal period. 29% of global share.
An estimated 75% of premature babies can be saved with cost-effective and feasible interventions globally

Figure 1. Overview of newborn health in India compared to global statistics.

staff managed the processes. Only 31% of milk banks had 3 or more dedicated lactation counseling staff; thus, the shortage of staff has been a stumbling block. Most of the milk banks pooled donor milk from multiple mothers. All the facilities used the Holder method of pasteurization. Processed donor human milk was used within a week or fortnight because of high demand in most of the sites. Milk collection was between 3 and 6 L every day in most of the facilities. The majority of milk banks reported a significant demand-supply gap. Hence, as a step to help mitigate the demand, select sites have recently developed satellite milk collection centers. The need to discard samples because of the presence of microbes after pasteurization was less than 5% at most study sites. (38)

Milk is predominantly collected at the facility level with one-third of the sites collecting milk from camps and homes as well. Donor milk collection in India is mainly from mothers of preterm infants, hospitalized mothers after delivery, and mothers who visit pediatric clinics for pediatric immunizations. These mothers are mostly cross-sectional donors. Longitudinal donation is not yet practiced in India. Even home-based collection of milk is not common and very few hospitals promote it. (38) Education for safe collection is imperative for home-based collection because of the potential risks of voltage fluctuations and electricity failures.

Only in-facility dispensation of donor human milk is promoted and once the infant goes home, there is no source of continuing human milk feeding if the mother cannot feed her child. (38)

Nearly 85% of milk banks in India have been established by nongovernment organizations, and only a handful had been supported by the government. (38) However, within the last 2 years nearly 50% of milk banks have been supported by the state governments. Rajasthan, one of the states with a high neonatal mortality rate, has supported the setting up of 10 milk banks during the last year. Similarly, the state government of Tamil Nadu has supported setting up 7 milk banks. The recurring cost of most milk banks is managed through hospital funds.

Various socioeconomic factors influence maternal motivation and willingness to donate breast milk. Katke and Saraogi reported that women at either end of the reproductive age spectrum and women with higher parity require more motivation to donate breast milk. Furthermore, milk donation can be promoted in India by teaching women about the benefits of donor milk. (39) A recent study surveyed mothers and influencers (fathers and grandmothers) about barriers to breastfeeding, kangaroo mother care, and providing donor human milk to preterm and sick neonates in India. (40) This study found limited awareness about human milk banks among mothers and influencers. Parents were

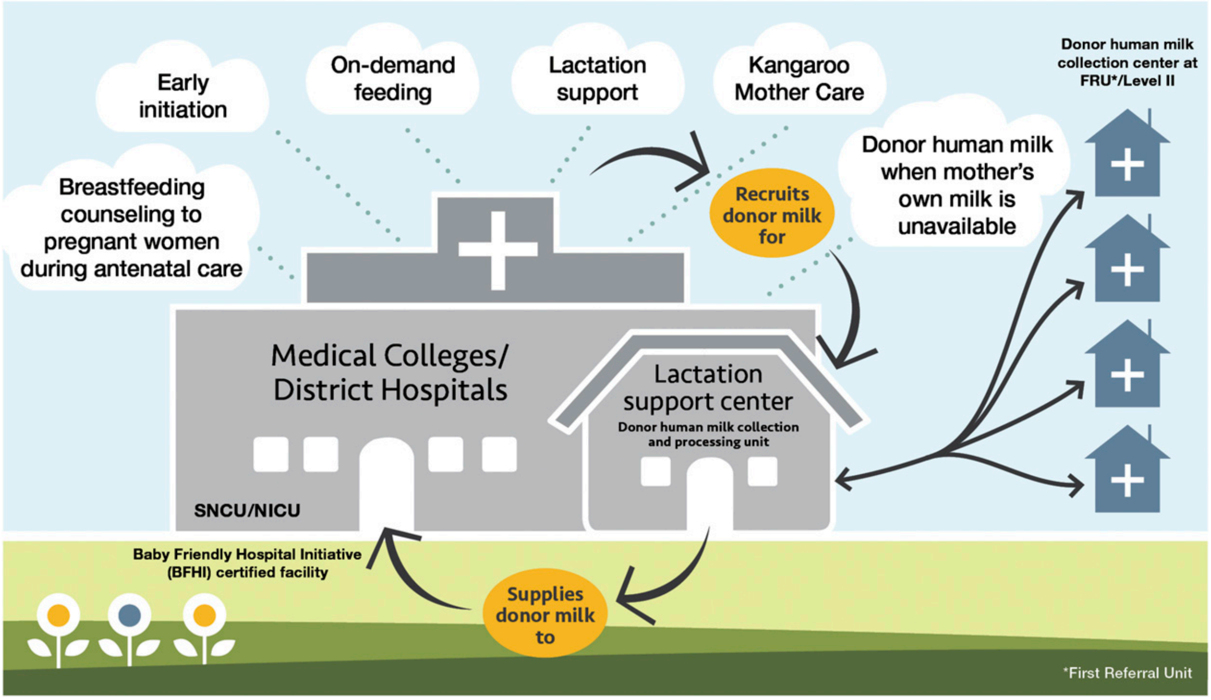
Early initiation
On-demand feeding
Lactation support
Kangaroo Mother Care
Donor human milk collection center at FRU*/Level II
Breastfeeding counseling to pregnant women during antenatal care
Recruits donor milk for
Donor human milk when mother's own milk is unavailable
Medical Colleges/ District Hospitals
Lactation support center
Donor human milk collection and processing unit
SNCU/NICU
Baby Friendly Hospital Initiative (BFHI) certified facility
Supplies donor milk to
*First Referral Unit

Figure 2. Mother Baby Friendly Initiative *Plus* model adapted for India's health structure. (Adapted from reference 36.)

supportive about donating milk once they learned that it was life-saving and did not compromise the supply to their own infant. However, some parents had safety concerns about the use of donor human milk and were not aware of milk banking processes. Most grandmothers were not comfortable with having their daughters/daughters-in-law donate milk or having their grandchild receive donor milk because they felt it may hinder supply for their grandchild. Most mothers shared that physicians counseled them about their dietary intake during antenatal care, but did not provide them with information about breastfeeding. Few mothers shared the challenges they faced with feeding their preterm and sick infants. Mothers who practiced kangaroo mother care were aware of its benefits. Respondents shared that wet nursing is an old practice. They found wet nursing to be helpful, as the infant receives human milk and they are assured that it is not harmful for the infant if practiced within the family. (40)

ROLE OF THE GOVERNMENT IN SCALING UP HUMAN MILK BANKING IN INDIA

The government of India has acknowledged the role that human milk banking can play in reducing neonatal mortality and morbidity and held the first national consultative meeting for formulating national guidelines on human milk banking in 2013. Subsequently, the Indian Academy of Pediatrics formulated a set of guidelines in 2013. (41)

The government of India highlighted the need for formulating operational guidelines with robust protocols and emphasis on implementation strategy, quality control mechanisms, monitoring, and accreditation. The Ministry of Health and Family Welfare took this initiative in 2014 and formed a group composed of human milk bank experts, neonatologists, regulatory officials, and quality and public health specialists to support this effort. Subsequently, the government launched the "National Guidelines on Lactation Management Centers in Public Health Facilities" in July 2017. (42) These guidelines are part of a program focusing on breastfeeding launched by the government of India called Mother's Absolute Affection (MAA). MAA in Hindi, the national Indian language, means mother. The vision of the government is to make breast milk universally available for all infants by establishing comprehensive lactation management centers (CLMC), lactation management units (LMUs) and lactation support units (LSUs) at the facility level. The CLMC model is based on the MBFI+ model (Fig 4).

The model builds on India's public health system which is a 3-tier system with primary, secondary, and tertiary levels of care. The district hospital is an essential component of the district health system and provides secondary level of care. Every district has a hospital that is linked to health facilities under the district such as subdistrict hospitals, community health centers, primary health centers, and health subcenters. Primary health centers are the cornerstone of rural health

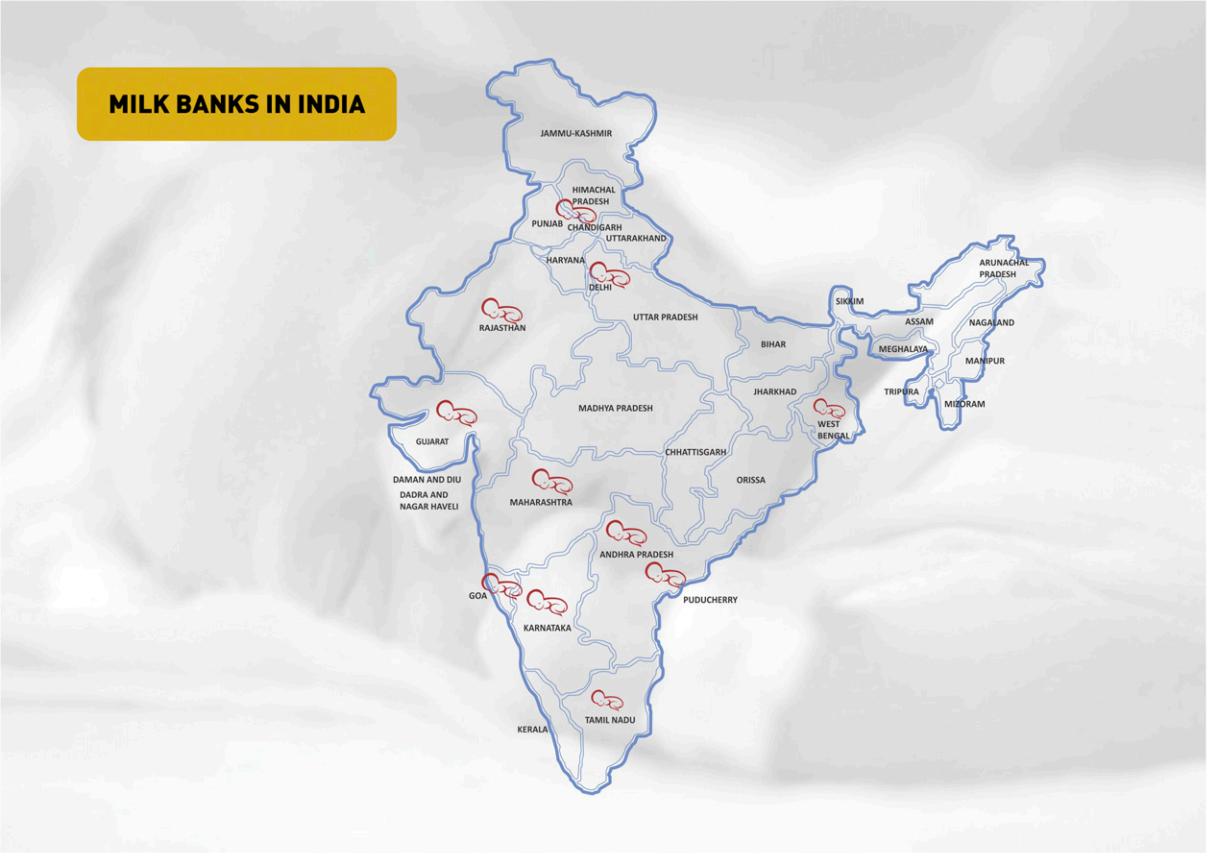

Figure 3. States with operational human milk banks in India.

services, providing basic essential newborn care. They cater to a population of around 30,000 with the help of a medical officer, pharmacist, and support staff. Community health centers, catering to a population of 120,000 people, are the first level where specialists are available. They aim to provide secondary level care with stabilization services for newborns. First referral units are being developed by upgrading selected community health centers and subdistrict hospitals where 24-hour emergency obstetric and child health services will be provided. (43) Currently, there are 715 functional special care newborn units, mostly at district hospitals, to reduce case fatality among sick newborns and to function as training centers for teaching newborn care skills. A large number of secondary and tertiary care units responsible for newborn care are usually within larger hospitals, many even higher than the district level such as at the medical college level.

SALIENT FEATURES OF THE NATIONAL GUIDELINES

LMCs are seen as an effort to promote the natural act of breastfeeding and ensure availability of safe donor human milk for sick infants when MOM is not available. A CLMC will be set up at tertiary care facilities/medical colleges with a functional NICU and high delivery load. This would function as a lactation support center to support breastfeeding, as well as to safely collect, process, and provide safe donor human milk. Subsequently, CLMCs will be set up at

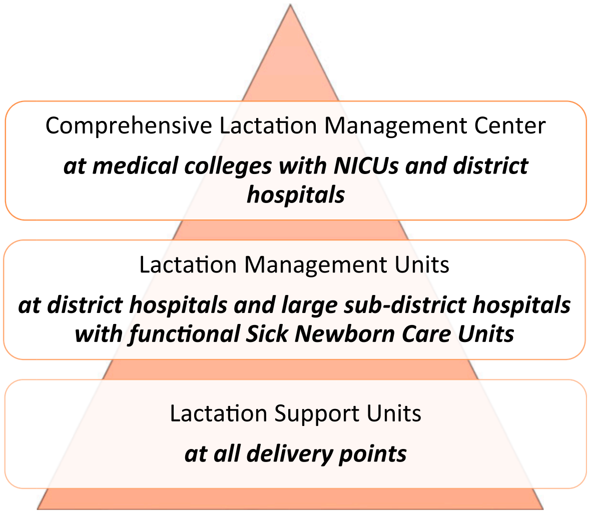
Comprehensive Lactation Management Center
at medical colleges with NICUs and district hospitals
Lactation Management Units
at district hospitals and large sub-district hospitals with functional Sick Newborn Care Units
Lactation Support Units
at all delivery points

Figure 4. Facility based lactation management at the three levels. (Reprinted from reference 42.)

district hospitals that fulfill the prerequisites for establishing one. These units will support breastfeeding mothers, encourage kangaroo mother care, and support the formation of LMUs at first referral units/subdistrict hospitals. These LMUs will facilitate the expression and collection of MOM for her infant's use. To maintain the continuum of care, LSUs will be established at all delivery points by forming a dedicated team of staff trained to provide round-the-clock breastfeeding support, lactation counseling, and kangaroo mother care support to mothers. (42)

The guidelines mandate informed consent by both the donor and the recipient. Donor milk will only be dispensed with a physician's prescription and is recommended to meet the short- and long-term needs of newborns admitted in NICUs/sick newborn care units with the following conditions: 1) prematurity, 2) low birthweight, 3) malabsorption, and 4) feeding intolerance.

Donating human milk will be a completely voluntary and nonincentivized activity, and this milk cannot be used for any commercial purposes. The government is working on developing a regulatory mechanism to prevent human milk commercialization.

Human milk donation and dispensation will be done only at specialized units within the CLMC with the highest regard for safety and meticulous approach to ensuring quality. The guidelines consist of evidence-based and standardized technical protocols for donor screening and collection, processing, storage, and dispensation of human milk. Ensuring the quality and safety of donor human milk is an important component of these guidelines. In addition, recommendations have been made to minimize the risk of donor human milk to recipients. The standards of quality have been stated in detail with a strong focus on hygiene and handling of milk. The guidelines enforce mandatory training of staff on a Hazard Analysis Critical Control Points system, which is a management system designed to address food safety from production to consumption.

A National Human Milk Bank has been established which will function as the national resource center to provide training, undertake quality audits, and ensure technical support to establish new CLMCs and LMUs. Regional and zonal reference centers will be established in each geographical zone at well-performing CLMCs, to assist the

TABLE 2. **Suggested Initiatives for Technical and Policy Leaders to Improve Access to Human Milk**

Improve government ownership to meet recurring costs, address personnel shortages, and enhance community mobilization.
Mandate availability of standard operating procedures at facilities for uniform process implementation and to ensure safety.
Establish one national and few zonal reference centers to develop stringent systems for monitoring and evaluation, accreditation and quality control.
Develop a strong regulatory framework and effectively implement the same to prevent commercialization.
Generate local evidence on the CLMC model by undertaking research to determine knowledge, practices, and perceptions related to the establishment of CLMCs in similar community settings and to explore the multidimensional aspects in opportunities and challenges for scaling up human milk banking in India.
Develop robust behavior change communication strategies related to breastfeeding, kangaroo mother care, and donor human milk targeted at mothers and influencers, starting from the antenatal period.
Provide skill-based training to medical practitioners and health care providers on the CLMC model.
Ensure counseling of pregnant women and lactating mothers by health-care providers and peer educators to promote early initiation of breastfeeding in the labor room.
Use mother support groups to create a suitable environment for continued and sustained breastfeeding.
Slowly eliminate wet nursing, an ancient and deep-rooted practice, by generating intensive awareness about its adverse effects.
Establish satellite centers attached to milk banks to recruit more donors to benefit more infants.
Extend the guidelines to the private sector to ensure that infants born in the private sector (about 60% rural and 70% urban areas) are also covered. (44)
Gather technical and policy leaders to discuss steps to ensure access to donor human milk for all infants in need whether in the hospital or at home.
Develop technologies that improve quality systems and are easy to use and cost-effective to help human milk banks run safely and effectively not only in India but other low-resource settings around the globe.

CLMC=Comprehensive lactation management center.

national resource center by serving as a technical resource for nearby CLMCs, LMUs and LSUs. (42)

THE WAY FORWARD

Some noteworthy initiatives in the recent past have been the use of the "green corridor" (organ donation van) in Rajasthan to transfer milk to needy NICUs from the collection centers in record time, as well as the establishment of a mobile van equipped with a breast pump and a refrigerator for collecting donor milk from mothers in the community in the state of Maharashtra. The Human Milk Banking Network of India has been established to share best practices and create awareness among health-care providers. Media engagement has also increased over the past year and the issue is well covered across multiple platforms.

As a next step, as policy and technical leaders work toward implementing these guidelines to ensure that all infants have access to human milk (both MOM and safe donor human milk), it will be imperative that the following initiatives are taken (Table 2).

Effective scale up of human milk banking systems in India has significant potential. Estimates suggest that 30% to 50% of neonates admitted to the NICU and 10% to 20% of full-term infants are in need of donor human milk to meet the short- or long-term lack of mother's milk. Increasing access to human milk has the potential to help approximately 5 million infants. When combined with enhanced breastfeeding methods, the impact could be 10-fold. (38)

As human milk banking systems expand and strengthen, this will not only have an impact on the immediate health of neonates but will also have long-term positive effects. India bears the highest global burden of neonatal births and deaths, therefore improvement in neonatal health indicators will help India and the world achieve their goal of reduced neonatal mortality and morbidity.

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American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the advantages and disadvantages of the use of donor human milk.

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Health Care and Societal Costs of Bronchopulmonary Dysplasia

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Education Gaps

Bronchopulmonary dysplasia (BPD) continues to affect a large portion of very low-birthweight infants; therefore, knowledge of the short- and long-term economic impact of BPD is necessary to gain a broader perspective of the disease.

Abstract

Despite significant technological advances and increasing survival of premature infants, bronchopulmonary dysplasia (BPD) continues to be the most prevalent major morbidity in surviving very low-birthweight infants. Infants with BPD are often sicker, require longer stays in the NICU, and accumulate greater hospital costs. However, care of the infant with BPD extends beyond the time spent in the NICU. This article reviews the costs of BPD in the health-care setting, during the initial hospitalization and beyond, and the long-term neurodevelopmental impact of BPD, as well as the impact on a family caring for a child with BPD.

Objectives After completing this article, readers should be able to:

1. Describe the short- and long-term costs for infants with bronchopulmonary dysplasic (BPD).
2. Describe the impact of BPD on the health-care system.
3. Compare the costs of infants and children with BPD to those without BPD.
4. Discuss the impact of BPD on the child's neurodevelopment.
5. Estimate the burden of BPD on the family unit.

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ABBREVIATIONS

BPD	bronchopulmonary dysplasia
GA	gestational age
RSV	respiratory syncytial virus
VLBW	very low-birthweight

INTRODUCTION

Approximately 1 in 10 infants is born prematurely in the United States. (1) In the year 2015 alone, there were more than 55,000 very low-birthweight (VLBW, <1,500 g) infant births. Although overall survival rates are improving, the number of VLBW infants with at least 1 major morbidity remains high. (2) Bronchopulmonary dysplasia (BPD) was initially described as a disease of premature infants by William Northway, Jr, in 1967, when potential ventilator injury and oxygen toxicity were recognized as modifiable factors in ameliorating the disease process. (3) Although we have gained considerable understanding of the pathophysiology of BPD since that time, it continues to be the most prevalent major morbidity affecting an estimated 22% to 45% of all VLBW infants in the United States. (2)(4) This article reviews the resource utilization and costs of BPD and the impact on the health-care system and family.

DIRECT MEDICAL COSTS AND HEALTH-CARE UTILIZATION

Birth Hospitalization

VLBW infants account for a large percentage of birth hospitalization costs. In a population-based study in California, VLBW infants comprised 0.9% of all birth hospitalizations but accounted for 35.7% of total costs. (5) As infants with BPD tend to be sicker and smaller, the costs for caring for these infants are comparatively increased. In low-birthweight infants (<2,500 g), Russell et al found that the single most expensive cause of morbidity based on average cost per discharge was BPD; infants with BPD had an initial hospitalization cost that was 16 times higher than the cost of infants without BPD. (6) The median cost for NICU hospitalization for infants with BPD was $102,000 (US dollars, 2001) per infant compared to a median of $36,800 for all infants less than 28 weeks' gestational age (GA) and $500 for uncomplicated newborns. Johnson et al found that in VLBW infants, BPD has the highest associated mean marginal costs compared to other significant morbidities (necrotizing enterocolitis, late-onset sepsis, brain injury). (7) The direct costs for those with BPD were 2.3 times higher than for those without BPD. Infants with BPD have significantly increased lengths of stay and hospitalization costs because of the greater number of procedures, greater duration of respiratory equipment use, and other advanced medical technologies in addition to increased risk of complications and comorbidities. (5)(8) These increased costs are reflected in prolonged hospitalization, with infants with BPD having an average length of stay 4 weeks longer, even after adjusting for birthweight and other risk factors. (9) Affected infants have an almost 6-fold increased risk of delayed discharge, defined as discharge after 42 weeks' postmenstrual age. (10) Although there is tremendous variability in what is included in the cost accounting studies (eg, facility fees, hospital fees, etc), infants with BPD consistently pose a significantly higher economic burden on the health-care system across times and multiple studies (Table).

The First 2 Years: Back to the Hospital and the Role of Respiratory Infections

Respiratory illnesses are the number 1 reason for hospital readmissions in premature infants. (11) As BPD is known to be an underlying cause of pulmonary dysfunction, infants with BPD are susceptible to respiratory infections as well as increased severity of illness; thus, they are at greater risk for hospital admissions during an illness. (11)(12) Many studies have demonstrated that infants with BPD, particularly those with moderate to severe BPD, have a significantly higher rate of rehospitalization for respiratory causes. (8)(11)(12)(13) In a population-based study of almost 1,600 infants at less than 33 weeks' GA, infants with BPD had increased rehospitalization rates during the first year of age (49%) compared with infants without BPD (23%). (8) Furthermore, there were significant differences in number of readmissions as well as length of stay during those subsequent hospitalizations.

A significant health-care burden for patients with BPD is respiratory syncytial virus (RSV). Although RSV often causes a self-limited respiratory infection for most infants, it is a leading cause of hospitalization in the first year for all infants, with rates of hospitalization reported at 16.9 per 1,000 infants of age 0 to 5 months and 5.1 per 1,000 infants of age 6 to 11 months. (14) It is recognized that BPD is a major independent risk factor for RSV disease leading to serious infections and hospitalizations. (15) Infants born preterm with BPD may be particularly vulnerable to RSV because of their history of underdeveloped or injured alveoli, pulmonary vasculature, and respiratory epithelium, which predisposes them to pulmonary edema with infection. (16) RSV infection in the context of BPD has been shown to lead to increased likelihood of hospitalizations, hospital length of stay, ICU admission, and need for mechanical ventilation. (17)(18)(19) Patients with BPD with RSV infections also have increased outpatient visits and higher total cost of care for the first 2 years of age. (20) A history of RSV infection in patients with BPD has a downstream effect on patient morbidity, leading to continued increased health-care utilization (outpatient visits, cost of care) at 5 to 7 years of age and also significantly worse pulmonary function at 8 to 10 years of age. (21) Palivizumab, a mouse monoclonal antibody product directed against an RSV protein, has been shown to be effective in reducing the burden of hospitalization in preterm infants, with RSV-related hospitalizations in preterm infants with BPD decreasing from 12.8% to 7.9%. (22) However, palivizumab remains an expensive therapy to administer and cost-effectiveness for various populations remains in question, though a stronger case can be made for preterm infants with BPD. (23)

Beyond the Second Year: Rehospitalizations and Outpatient Visits

Rehospitalization rates in patients with BPD continue to be comparatively higher beyond the initial year with an increased risk for rehospitalization and more frequent outpatient visits. (13) Although most infants will not require oxygen beyond 2 years of age, indicating clinical improvement, up to 25% will continue to have respiratory complications into young adulthood. (12)(24) Children and adolescents with a history of BPD are more often diagnosed with asthma (26.9% vs 11.8%; *P*<.0001) and psychiatric illnesses (such as depression, anxiety, attention-deficit/hyperactivity disorder) leading to increased health-care utilization. (25) In a Quebec study comparing a preterm BPD cohort and a preterm respiratory distress syndrome cohort over 16 to 25 years, the costs of medical services and total health-care costs per person annually was significantly increased in the BPD cohort ($13,472 vs $10,719; *P*=.02; expressed in 2008 Canadian dollars). (25)

Durable Medical Equipment

In a multicenter study, approximately one-third of infants with BPD of any severity were sent home with oxygen

TABLE. **Selected Studies Outlining the Resource Utilization and/or Cost Associated With BPD**

REFERENCE	YEAR PUBLISHED	POPULATION	TIME HORIZON	RESOURCES	COSTS/CHARGES	NOTES
Patel et al (26)	2016	N=254 VLBW Source: Prospective single center, admitted to the NICU 2008-2012 Country: USA	Birth hospitalization	Although the LOS is not directly reported, the authors do provide a cost per day and thus it could be calculated; additionally, there is a report on breakdown of different services used between the 2 groups (see Table 3 in Patel et al.)	Cost/charges: Costs Currency: US dollars, 2014 Median cost for BPD $269,004 (IQR:204,606-331,552) compared to $117,078 (IQR 90,496-162,017) (*P*<.001) In an adjusted analysis, BPD increased costs by $41,929 compared to non-BPD patients Source of costs: hospital data and cost accounting system includes direct and indirect hospital costs Facility fees: included Professional fees: included (based on physician payments) Parent costs: not included Other: N/A	Prospective cohort Table 3 of this article by Patel et al provides a detailed description of the total costs and the individual sub-costs (e.g. hospital direct costs, physician costs, and NICU cost per day) Adjustment: propensity score for BPD, race/ethnicity, gender, gestational age, and small for gestational age
Johnson et al (7)	2013	N=425 VLBW Source: Single center Country: USA	Birth hospitalization	LOS: BPD: Mean 94±31 days compared to 46±19 days w/o BPD (*P*<.001)	Cost/charges: Costs Currency: US dollars, 2009 Mean 103,151±43,482 compared to 44,465±23,300 (*P*<.001) BPD cost is $31,565 higher compared to no morbidity when adjusted for GA, sex, birthweight, race/ethnicity, and primary payer (*P*<.001) Source of costs: Hospital data and cost accounting system using direct hospital costs for each billable item Facility fees: included Professional fees: Not included Parent costs: Not included Other: N/A	Adjusted for birthweight, GA, and sociodemographic characteristics

Continued

TABLE. **(Continued)**

Reference	Year Published	Population	Time Horizon	Resources	Costs/Charges	Notes
Landry et al (25)	2012	N=3,442 (with BPD=773; RDS without BPD=2,669) Source: Provincial health administrative databases from Quebec (infants born with RDS and/or BPD between 1983-1992) Data was extracted through March 2008 for follow-up Country: Canada	16- to 25-year follow-up (mean duration 19.3 y for BPD and 17.6 y without BPD)	Health-care utilization and costs Table 2 in the article by Landry et al represents the health-care utilization data Hospitalizations: (mean±SD) BPD: 5±7.3 w/o BPD: 2.9±3.3 ($P<.0001$) ED visits (per subject; mean±SD): BPD: 15.4±18.9 w/o BPD: 12±14.5 ($P=.0002$)	Cost/charges: Costs Currency: Canadian dollars, 2008 Total cost per person-year (mean±SD): BPD: $13,472±527 w/o BPD: $10,719±625 ($P=.02$) Pharmaceutical costs (from 1997 only): BPD: $175±88 w/o BPD: $101±23 ($P=.06$) Source of costs: Administrative data Facility fees: Included Professional fees: Included Parent costs: Not included Other: Pharmaceutical costs	Infants were identified using ICD-9 codes for BPD, RDS, and prematurity. Hospitalization costs were based on estimates from the Canadian Institute of Health Information and Health Canada Higher diagnosis of asthma (11.13 vs 4.55 diagnosis per patient-year; $P<.0001$) There is no term equivalent comparison group (just former preterm infants with and without BPD) There was also an increased use of respiratory and neurologic/psychiatric drugs in a subset of the cohort with BPD compared to those w/o BPD)
Stroustrup et al (27)	2010	N=9,542,032 hospitalizations (1.53% of which were <1,500 g at birth) Source: NIS HCUP, 1993–2006 Country: USA	Birth hospitalization	LOS and charges	Cost/charges: Charges Currency: US dollars, year of currency not stated There are no exact cost and LOS estimates in the published article, but the authors give % changes over time: 3.9% annual increase (1993–2006) in LOS for patients with BPD; only 2% when adjusted for VLBW incidence ($P<.0001$) 4.9% annual increase (1993–2006) in charges for patients with BPD; only 2.9% when adjusted for VLBW incidence ($P<.0001$) Facility fees: Included Professional fees: Not included Parent costs: Not included Other: N/A	NIS samples 20% of US hospital discharges and is weighted to approximate population BPD identified using the ICD-9 code 770.7 Limited to patients <1,500 g birthweight and those who received noninvasive mechanical ventilation or continuous invasive mechanical ventilation ≥96 hours based on procedure codes Both univariate and multivariable analyses performed (4 different model adjustments were done) Goal of the study was to assess trends over time for incidence of BPD, LOS, and charges

Continued

TABLE. **(Continued)**

Reference	Year Published	Population	Time Horizon	Resources	Costs/Charges	Notes
Russell et al (6)	2007	N=9,400 (7,100–11,700) with BPD and 204,600 (186,800–222,300) without BPD Source: NIS HCUP, 2001 Country: USA	Birth hospitalization	LOS was determined in this study, but not directly comparing those with BPD to those without (however, there is LOS comparing normal newborns to preterm/low birthweight)	Cost/charges: Costs (charges were converted to costs using cost-to-charge ratios) Currency: US dollars, 2001 (presumed year, not explicitly stated) Mean 116,000 (95% CI=102,200–129,900; median=102,000) for BPD compared to 16,900 (95% CI=15,200–18,600; median=6,300) without BPD Source of costs: Administrative data Facility fees: Included Professional fees: Not included Parent costs: Not included Other: N/A	NIS samples 20% of US hospital discharges and is weighted to approximate population Attempted to minimize the overlap from inter-hospital transfers during the birth admission (80% of births involved no hospital transfer) BPD identified using the ICD-9 code 770.7 All patients who were defined as preterm/low birthweight (<2,500 g) were included in this analysis likely decreasing the mean/median cost of hospitalization in the non-BPD group
Smith et al (8)	2004	N=1,597 (14.9% with BPD) Source: Northern California Kaiser Permanente Medical Care Program, 6 level III facilities (Neonatal Minimal Dataset linked to California birth certificates and Kaiser follow-up); 1995–1999 Country: USA	Rehospitalization in the first year after birth among infants with BPD (born <33 weeks)	Rehospitalization rates LOS is included for the birth hospitalization	Cost/charges: N/A (resources only) Currency: N/A 49% rehospitalization rate in patients with BPD compared to 23% in patients without BPD (*P*<.0001) Mean number of rehospitalizations per infant was 2.2±1.9 (BPD) vs 1.6±1.1 (w/o BPD) (*P*=.0012) Mean LOS of 12.7±27.5 days (BPD) vs 6.4±9.4 days (w/o BPD) (*P*=.0036) Birth hospitalization LOS: 92.8±37.3 days (BPD) vs 38.4±20.6 days (w/o BPD) Source of costs: Administrative data Facility fees: N/A Professional fees: N/A Parent costs: N/A Other: N/A	Limited to those who survived to first birthday, had follow-up care at Kaiser, and did not have any major anomalies Table 1 of the study provides additional information on resource utilization during the birth hospitalization (eg, duration of ventilator and oxygen use; % of comorbidities such as NEC, ROP, and IVH) No risk factors identified among patients with BPD who were and were not readmitted

Continued

TABLE. **(Continued)**

Reference	Year Published	Population	Time Horizon	Resources	Costs/Charges	Notes
Greenough et al[a] (28)	2002	N=235 (88 received supplemental oxygen) Source: Born in 1 of 4 NICUs between July 1994 and July 1997 Country: United Kingdom	Readmissions and primary care use in the first 2 years after birth in infants with BPD (born <32 weeks) discharged with oxygen compared to infants with BPD with no support BPD defined as oxygen dependence beyond 28 days after birth in this study	Outpatient visits, community care, readmissions (resources and costs) Routine health-care visits were not recorded	Cost/charges: Costs, using the NHS website 1999 reference costs) Currency: British pounds, 1999 Readmissions per infant/LOS per infant: Median (range) Home oxygen group (n=88) – 2 (0-20)/7 days (0-131) w/o home oxygen group (n=147) –1 (0-20)/3 days (0-282) $P<.05$, $P<.01$ Total costs in the 2 years postdischarge: Mean (range) Home oxygen group (n=88) – 6,802 (896–85,831) w/o home oxygen group (n=147) – 4,881 (95–58,444) $P<.001$ Facility fees: Included Professional fees: Included Parent costs: Not included Other: N/A	Detailed review was performed of postdischarge records in the first 2 years after birth The costs are broken down into the following categories: Primary care total Primary care respiratory related Primary care drugs Hospital drugs Hospital stay Outpatient attendance Of note, these investigators have published 2 other analyses on this cohort: 1)@Pre-school health-care utilization by home oxygen status (n=190) – Greenough et al, 2006 (24) 2)@School age outcomes by admission status with RSV – Greenough et al, 2009 (29)
Greenough et al[a] (20)	2001	N= 235 Source: Born in 1 of 4 NICUs between July 1994 and July 1997 Country: United Kingdom	Readmission with proven RSV infection in the first 2 years after birth in infants with BPD (born <32 weeks) BPD defined as oxygen dependence beyond 28 days after birth in this study	Outpatient visits, community care, readmissions (resources and costs) Routine health-care visits were not recorded	Cost/charges: Costs, using the NHS website (1999 reference costs) Currency: British pounds, 1999 Readmission rate per infant: RSV group (n=45) – 5.4 Probably bronchiolitis (n=24) – 2.8 Other respiratory (n=60) – 3.1 Nonrespiratory (n=106) – 0.6 ($P<.001$ for between-group comparison) Total costs in the 2 years postdischarge: mean (95% CI) RSV group (n=45) – 12,638 (8,041; 17,235) Probably bronchiolitis (n=24) – 6,059 (3,427; 8,690) Other respiratory (n=60) – 5,683 (3427; 6775) Nonrespiratory (n=106) –2,461 (2,074; 2,849) ($P<0.001$ for between-group comparison) Facility fees: Included Professional fees: Included Parent costs: Not included Other: N/A	Detailed review was performed of postdischarge records in the first 2 years after birth The costs are broken down into the following categories: Primary care total Primary care respiratory related Primary care drugs Hospital drugs Hospital stay Outpatient attendance

Continued

TABLE. **(Continued)**

Reference	Year Published	Population	Time Horizon	Resources	Costs/Charges	Notes
McAleese et al (30)	1993	N=59 Source: Dartmouth-Hitchcock Medical Center, 1981–1989; infants with BPD who were discharged with oxygen; data obtained from hospital billing office Country: USA	Birth hospitalization and home oxygen therapy	Birth hospitalization (LOS and cost) Home oxygen therapy cost Financial and emotional stress on the family	Cost/charges: The article is not clear as it appears to use the words 'charges' and 'costs' interchangeably Currency: US dollars, 1989–1990 Birth hospitalization: Median birth hospitalization duration 120 days (range: 30–772 days) Mean birth hospitalization cost per patient: $197,668 (median $172,817, range $43,364–$864,594) Mean self-pay for hospital bill $14,103 Median out of pocket expenses $1,624 (range $267–$8,017) (travel, lodging, phone bill) Postdischarge: Home oxygen duration median 92 days (range: 9–577 days) Cost of oxygen and related equipment median $2,250 (range: $475–$9,000) Facility fees: Included Professional fees: Included Parent costs: Included (using parent interviews; parental wage losses were included) Other: N/A	Combination of hospital records as well as parental records and regional charges were used Distribution of costs 82% – hospital charges 12% – physician fees 5% – community hospital charges 1% – parental expenses Interviews of parents provided parental expenses during infant hospitalization Financial and emotional impact of home care was assessed via a questionnaire Home oxygen therapy costs were obtained as average charges from suppliers in the region

The table breaks down some of the elements of costs and summarizes the economic burden. BPD=bronchopulmonary dysplasia; ED=emergency department; GA=gestational age; HCUP=Healthcare Cost and Utilization Project; ICD-9=International Classification of Diseases, Ninth Revision; IQR=interquartile range; IVH=intraventricular hemorrhage; LOS=length of stay; N/A=not available; NEC=necrotizing enterocolitis; NHS= National Health Service; NIS=National Inpatient Sample; RDS=respiratory distress syndrome; ROP=retinopathy of prematurity; RSV=respiratory syncytial virus; VLBW= very low birthweight.

[a] *Represents the same cohort of patients with different focus and period of analysis.*

supplementation. (24) Infants categorized with either moderate or severe BPD likely account for most of these cases, as they are discharged with oxygen supplementation 57% to 68% of the time. (31)(32) It is important to note that home oxygen use is largely institution dependent, with a large study of 117 centers finding that home oxygen use ranged from 7% to 95% in infants requiring respiratory support at 36 weeks' postmenstrual age. (32) Infants who were oxygen dependent had outpatient visits, specialist visits, and prescription costs approximately 3 times greater than infants sent home without oxygen from 2 to 4 years of age. (24) As most children no longer required continuous supplemental oxygen beyond the second birthday, this represents a continued increased health-care cost and respiratory morbidity beyond just receiving oxygen supplementation. These differences in health-care utilization continued through school age. (33)

Given that prolonged ventilation plays a significant role in the development of BPD, infants with severe BPD are at increased risk for tracheostomy placement with or without ventilator dependence. Tracheostomy may be a result of pulmonary disease that is dependent on positive pressure ventilation, consequences of prolonged intubation (such as subglottic stenosis, vocal cord paralysis, granulation tissue), or airway anomalies (such as laryngotracheomalacia). A large multicenter study found that 0.1% of all NICU infants required a tracheostomy over a 16-year period, with BPD being the number 1 diagnosis associated with the procedure (45%). (34) Another study from 27 centers found that 13.5% of infants with severe BPD required a tracheostomy and 20.4% of infants with severe BPD required a tracheostomy or died before discharge. (35) Infants with tracheostomies are either discharged from the hospital or sent to a care facility after receiving extensive family education and multidisciplinary care coordination by the medical team to ensure safety. Once a tracheostomy is placed, the median time to decannulation was 436 to 479 days (range 48–1,611 days). (36) Furthermore, health-care utilization in the 5 years following tracheostomy placement in children is increased, including total time of hospitalization (mean±SD, 32.3±65.9 days) and risk of at least 1 readmission within 30 days (45.1%). (37) The use of technology can increase both direct medical costs (equipment, supplies, nursing care, outpatient visits, hospitalizations, prescriptions) and nondirect costs (electricity, water, family stress, loss of income).

BPD AND CHILD NEURODEVELOPMENT

Numerous studies have found that BPD is an independent risk factor for poor developmental outcomes, low IQ, and cerebral palsy. (12)(38) Children with moderate to severe BPD have a lower developmental quotient and more developmental disabilities (defined as developmental quotient less than 2 SD below mean, severe cerebral palsy, bilateral blindness, or severe hearing deficit) compared to those with or without mild BPD. (39) Infants with BPD often have more prolonged periods of hypoxemia, or apnea, associated with the need for increased ventilator days compared to peer infants without BPD. This severity of illness likely affects brain development of the premature infant. In cases of severe BPD, movement disorders similar to chorea and akathisia have been described as early as the third month of age with an autopsy in 1 patient demonstrating hallmarks of hypoxic brain injury. (40) Moreover, infants with BPD have poor physical growth compared to peers with lower mean weight and head circumference. (38)(41) Thus, the effects of BPD on neurodevelopment is likely multifactorial, related to underlying pathophysiology of BPD, growth failure, and environmental factors (such as socioeconomic status and parental education).

The delay in neurodevelopment can be detected early with a significantly increased number of infants with BPD having sensorineural conductive hearing loss compared to controls requiring tympanostomy tube placement (22.1% vs 7.7%). (42) Another study demonstrated that at 10 months of age, infants with BPD had poor hand-eye coordination and perception and intelligence compared to infants with mild BPD or without BPD. (43) These differences persisted at age 5.5 years with poor visual-spatial development along with deficits in cognition. (44) Deficits are also apparent in language development as infants with BPD have lower receptive language skills starting at 3 years of age with increased enrollment in speech and language therapy by 8 years of age compared to peers without BPD. (45) By school age, children with BPD were more likely to be enrolled in special education classes with deficits in reading, mathematics, and gross motor skills, even after correcting for neurologic risk factors. (46) Greater severity of BPD was also associated with lower school achievement, lower IQ, increased therapy needs (occupational, physical, speech), and special education enrollment. In particular, those requiring a tracheostomy had significantly more adverse developmental outcomes. (47) With these complications, it is not surprising that adults with a history of preterm birth and BPD were less likely to have access to higher education and more likely to be unemployed. (48)

In an estimate by the Centers for Disease Control and Prevention, average lifetime costs for 4 different developmental disabilities (mental disabilities, cerebral palsy, hearing loss, and vision impairment) ranged from $417,000 to $1,014,000 (2003 US dollars) per person. (49) As individuals with BPD are at higher risk of being affected by these disabilities both through childhood and as adults, the economic costs continue to be comparatively increased throughout their lifetime. The report further specifies that lifetime indirect costs (ie, productivity losses, decreased functional participation) reflects up to 81% of total lifetime costs. When looking at direct medical expenditures alone, children who have more than 1 disability will have substantially higher associated costs. In a comparison of children with cerebral palsy, those who also had intellectual disability had 1-year mean medical expenditures 2.5 times the amount of those with a single diagnosis of intellectual disability or cerebral palsy. (50) Even with 1 diagnosis, the mean medical expenditure in 1 year was 10 times higher than the control population without cerebral palsy or intellectual disability.

FAMILY BURDEN

Studies have shown that there are increased parental stressors when an infant is born prematurely or with low birthweight. (51)(52) Psychological distress is mainly manifested as symptoms of depression, anxiety, and posttraumatic stress both during and after a NICU admission. (52) Up to 40% of mothers of very preterm infants report significant depression based on the Edinburgh Postpartum Depression

Scale compared to 10% to 15% of postpartum women overall. (53) As BPD infants tend to have more complications and a prolonged hospitalization, mothers of infants with BPD often have more severe negative symptoms. Caregivers are also more likely to have negative symptoms during the first 2 years of age if the child is frequently ill, and requires more outpatient visits and health-care utilization. (54) Studies have shown that personal, family, and financial stressors are more pronounced when the school-age child has lower IQ scores and more severe neurodevelopmental outcomes. (55)(56) In a prospective longitudinal study Singer et al compared mothers of VLBW infants with BPD, VLBW infants without BPD, and term infants from birth through adolescence. (56)(57) Over time, mothers of VLBW infants with BPD had increased personal, family, and financial stress, as well as lower attainment of additional education, whereas mothers of VLBW infants without BPD had similar outcomes to term mothers in most categories. Financial stressors can be a direct result of loss of wages, with up to 42% of families of infants with BPD discharged with oxygen supplementation losing wages in order to provide home medical care to their child. (30) Financial strain directly affects parental stress, with familial socioeconomic status being a significant risk factor for greater stress for any family independent of the child's health status or IQ. (56)

The impact on the family is best portrayed from the parents' own experience. As part of understanding the family burden of NICU parents, one of the coauthors (A.N.) led a video project to highlight the NICU parent perspective. Parents talked about what life is like with their children years after the NICU. In this 6-minute video (https://youtu.be/TRGKWm2DBbA), the impact of having a former premature infant with special health-care needs is communicated eloquently and clearly by the family (Fig).

Figure. Chris and Denise Van Dis with their twins, Natalie and Caleb, who were born at 24 weeks' gestation and had bronchopulmonary dysplasia. Click this link (https://youtu.be/TRGKWm2DBbA) to watch a 6-minute video of the parents' account of their personal experience of bringing home 2 former preterm infants with BPD.

CONCLUSIONS AND IMPLICATIONS

BPD is the most prevalent major morbidity in surviving VLBW infants. The economic burden stems from increased health-care costs starting with the birth admission and persists through childhood and into adulthood. The costs are increased both in a setting of relatively routine disease states (eg, RSV infection), as well as with disease severity (eg, patients with tracheostomies). In addition, there is a significant impact on the family unit of patients with BPD, with respect to both psychosocial and financial stressors. The burden of BPD that is imposed on the health-care system and the family, in combination with the association of BPD and worse neurodevelopmental outcomes, produces a substantial cumulative societal cost. When considering strategies in BPD reduction (ie, delivery room interventions, lung protective ventilation approaches, novel medications, quality improvement interventions), the return of investment calculus should take into account the annual economic impact of 12,100 infants diagnosed with BPD (22% of VLBWs, low estimate) per year in the United States and their lifetime "cost" to those individuals and their families, health-care system, and society.

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American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the prognosis, long-term complications, and permanent sequelae of bronchopulmonary dysplasia.

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1. Your NICU is forming a multidisciplinary team specifically focused on the care of the very preterm neonate. As you plan for resource allocation, you are reviewing studies on very low-birthweight infants. Which of the following morbidities experienced by these infants has been associated with the highest mean marginal cost?
   - A. Intraventricular hemorrhage.
   - B. Bronchopulmonary dysplasia (BPD).
   - C. Late-onset sepsis.
   - D. Necrotizing enterocolitis.
   - E. Brain injury.
2. A 25-week gestational age infant is nearing discharge after a prolonged initial NICU stay. The infant was diagnosed as having BPD at 36 weeks' postmenstrual age, but is now breathing room air. As you counsel the parents on what to expect in the coming months, they ask about the possibility of rehospitalization. Which of the following statements regarding preterm infants and hospital readmission is correct?
   - A. Respiratory illnesses are the number 1 reason for hospital readmissions in premature infants, and patients with BPD are at higher risk for such readmissions.
   - B. Although prolonged NICU hospitalizations are not desirable, a benefit of a long hospital course in very preterm infants is that their risk of readmission within the first year is lower than that for term or late preterm infants.
   - C. Although preterm infants are just as likely to have illnesses that might lead to hospitalization, the rates of hospital readmission in the first year are similar to or less frequent than term infants, due to parental avoidance of the health-care system.
   - D. BPD is not an independent risk factor for increased readmission during the first year after birth.
   - E. The main reason for readmission in infants with BPD is patent ductus arteriosus ligation.
3. As a premature infant is getting ready for discharge, you are counseling the parents about the potential benefits of palivizumab for respiratory syncytial virus (RSV) prophylaxis. Which of the following statements regarding this practice is correct?
   - A. RSV has a consistent risk profile for both term and preterm infants during the first year, with similar rates of hospitalization during each month after birth.
   - B. Although RSV infection can be more serious in infants with BPD, hospitalization for an RSV infection is now rare, because of the growing efficacy of herd immunity from vaccinations.
   - C. It is recognized that BPD is a major independent risk factor for RSV disease leading to serious infections and hospitalizations.
   - D. Although RSV infection can cause serious illness in infancy, there are no associated long-term effects, other than recurrent wheezing which may last up to about 3 years of age.
   - E. Palivizumab is recommended for all preterm infants of less than 34 weeks' gestational age regardless of whether there was a history of BPD.
4. A female infant born at 25 weeks' gestational age is now 2 years old and being seen in the follow-up clinic. The infant had a history of BPD and went home receiving oxygen therapy, but oxygen therapy was discontinued since 6 months of age. She is now meeting developmental milestones, with no hospitalizations in the past year. Which of the following statements regarding this and similar patients is correct?

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A. This patient is not truly categorized as having BPD, because she does not require oxygen at 2 years of age.
B. Children with a history of BPD are more often diagnosed with asthma and psychiatric illnesses such as depression and anxiety.
C. Rates of readmissions to the hospital and outpatient visits for patients with BPD become similar to the general population after the first year.
D. In most population-based cohort studies, up to 75% of patients diagnosed with BPD in the NICU will require oxygen again in childhood after they turn 2 years old.
E. By young adulthood (~18 to 22 years of age), the rates of respiratory complications in patients who had BPD are less than 5%.

5. An infant born at 25 weeks' gestational age has BPD and is now 4 months old in the NICU. He continues to require oxygen therapy, with occasional need for positive pressure ventilation. As you are discussing further management, you discuss the possibility of tracheostomy. Which of the following statements regarding supplemental oxygen and other therapies for patients with BPD is correct?

A. Although tracheostomy is a relatively common procedure in the NICU (~10% of all patients), it is relatively less common for patients with BPD (~1% of infants with severe BPD) because of the transient nature of the disease.
B. Tracheostomy may be a result of pulmonary disease dependent on positive pressure ventilation, consequences of prolonged intubation (such as subglottic stenosis, vocal cord paralysis, granulation tissue), or airway anomalies (such as laryngotracheomalacia).
C. Most tracheostomies for this condition are short-lived, with median time to decannulation being 30 to 45 days, depending on the cohort.
D. Health-care utilization in the 5 years after tracheostomy placement is less than that among those who do not receive tracheostomy, due to the benefit of relative stability of airway management and decreased need for acute care hospitalization.
E. Although there is an added immediate cost for the procedure of tracheostomy, there is generally an overall cost savings in early infancy (~0 to 5 years of age) for both direct and indirect costs, due to reduction in readmission after the procedure.

Health Care and Societal Costs of Bronchopulmonary Dysplasia

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Control of Breathing and Apnea of Prematurity

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Education Gaps

1. The short- and long-term morbidities associated with apnea of prematurity continue to be a clinical concern.
2. Optimizing therapeutic approaches to apnea of prematurity depend on understanding the pathophysiologic mechanisms of the condition.

Abstract

Apnea of prematurity is a significant clinical problem manifested by an unstable respiratory pattern leading to bradycardia and hypoxemia. Most of these apneas are idiopathic and represent a physiologic manifestation of an immature control of breathing and adaptation to extrauterine life. In extremely preterm infants, this unstable breathing pattern superimposed on an immature lung that is injured by inflammation and infection may lead to frequent and profound episodes of intermittent hypoxemia. These cardiorespiratory events during early postnatal life may be associated with both short- and long-term morbidity. In this review the author discusses the most important pathophysiologic mechanisms responsible for periodic breathing and apnea in preterm infants, as well as the diagnostic assessment and therapeutic interventions that help to stabilize breathing in this unique population.

Objectives After completing this article, readers should be able to:

1. Describe the pathophysiologic mechanisms underlying periodic breathing and apnea of prematurity.
2. Understand the role of the peripheral chemoreceptors and the carbon dioxide apneic threshold in the pathogenesis of apnea and periodic breathing.
3. Understand the negative effect of inflammation and infection on respiratory development, which contributes to worsening apnea and aggravation of intermittent hypoxemic events in extremely preterm infants.
4. Describe the most important therapeutic approaches to apnea of prematurity.

AUTHOR DISCLOSURE Dr Alvaro has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CO_2	carbon dioxide
CPAP	continuous positive airway pressure
FRC	functional residual capacity
LCR	laryngeal chemoreflex
NIPPV	nasal intermittent positive pressure ventilation
REM	rapid eye movement
SpO_2	pulse oximetry

INTRODUCTION

Apnea of prematurity is one of the most common diagnoses in neonatology and has become one of the most important clinical problems in the NICU. This type of apnea should not be considered a pathologic state but rather a physiologic manifestation of an unstable breathing pattern, which reflects the immaturity of the control of breathing and adaptation to extrauterine life.

The prevalence of apnea increases exponentially with decreasing gestational age and is present in almost 100% of infants with less than 29 weeks of gestation. (1)(2) From a physiologic point of view, it is not the apnea but its effect on oxygenation and heart rate that alter the well-being of the patient. Recent studies have shown an association between apnea and intermittent hypoxia with short- and long-term consequences such as retinopathy of prematurity, bronchopulmonary dysplasia, and neurologic disabilities. (3)(4)(5) This article will present a review of respiratory control with an emphasis on apnea of prematurity. The physiologic disorders of the control of breathing, which predispose infants to apnea, as well as the most relevant aspects of the treatment necessary for these patients will be identified.

DEFINITION

Apnea is the cessation of respiratory air flow. It is considered pathologic if it is prolonged (>20 seconds) or if it is associated with bradycardia, cyanosis, pallor, or hypotonia. (1)(2) However, what best defines apnea is not the duration of the respiratory pause but the physiologic consequences that result from that pause, such as the severity of bradycardia and hypoxemia. For example, very low-birthweight infants usually develop significant bradycardia and hypoxemia after respiratory pauses of less than 10 seconds in duration. The term “apnea of infancy” refers generally to pathologic apneas that begin in newborns of more than 37 weeks of gestational age. The term “apnea of prematurity” is reserved for apnea that occurs in preterm infants and which are usually resolved at 37 weeks of gestation. (2)

Periodic breathing is another form of central apnea characterized by ventilatory cycles of 10 to 15 seconds, with pauses of 5 to 10 seconds that are commonly observed in preterm infants and in adults traveling to high altitudes. Its physiopathogenic root could be the same as that of apnea, which would be a more advanced step in the basic disturbance that induces periodic breathing. The cyclic changes in respiratory rate and tidal volume observed during periodic breathing are partly due to the instability of the respiratory center, which in a more advanced degree would appear as apnea. (6) In support of this idea, several studies have shown that prolonged apneas (>20 seconds) associated with bradycardia and hypoxemia are not isolated events but are usually preceded by other short-lived apneas and by decreases in respiratory frequency and minute ventilation. (6)(7) The fact that the incidence of periodic breathing and apnea decreases with postnatal age, with the administration of methylxanthines and with an increase in oxygenation, supports this hypothesis. In patients with inadequate functional residual capacity (FRC), periodic breathing may be accompanied by significant oxygen desaturations which, if they persist, may result in the so-called intermittent chronic hypoxia.

CLASSIFICATION

Traditionally, apneas have been classified as central, obstructive, or mixed, depending on the presence of respiratory efforts and upper airway obstruction (Fig 1). These differences have become less clear with the evidence that central apneas can occur with airway obstruction (silent obstruction). Central apneas are characterized by lack of respiratory efforts, measured by the diaphragmatic activity or by chest or abdominal movements. Obstructive apneas are characterized by absent respiratory flow, measured usually at the nasal level, but with respiratory efforts present throughout the pause. These apneas are rare, usually short (<10 seconds) and occur generally before or after generalized body movements. Longer obstructive apneas are usually observed in newborn infants with Pierre-Robin syndrome (mandibular hypoplasia), in neonates with bronchopulmonary dysplasia, and in those with severe neurologic problems such as intracranial bleeding, hydrocephalus, and severe asphyxia. Mixed apneas are the most common type and are characterized by a central and obstructive component. These apneas may go undetected with thoracic impedance monitors and be detected only by the presence of bradycardia or hypoxemia. Because most mixed apneas begin with a central component and are followed by airway obstruction, their frequency progressively increases with the duration of apnea (Fig 2). (7)

PATHOGENESIS

Most premature infants have the basic tools to breathe spontaneously and with relative continuity. However, significant disadvantages, such as the immaturity of respiratory control, inability to maintain adequate FRC due to the high distensibility of the rib cage, propensity to airway obstruction, and difficulties in coordinating respiration with suction and swallowing, predispose premature infants to breathe irregularly, periodically, and with frequent apneas.

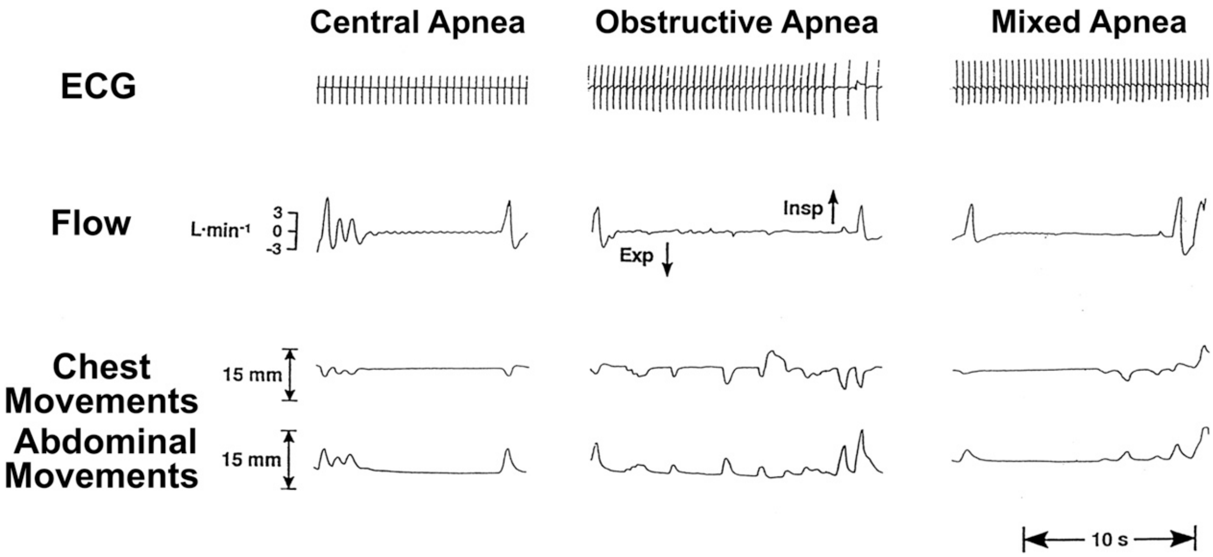

Figure 1. Examples of types of apnea diagnosed with the traditional method. Apnea is termed *central* when respiratory efforts are absent, *obstructive* when respiratory efforts are present continuously, and *mixed* when elements of both are seen. ECG=electrocardiography.

Periodic breathing and apnea are clearly a disorder of the control of breathing but the precise mechanisms are not very clear. In premature infants, the negative feedback system that controls respiration is affected by the anatomic and physiologic immaturity that affects many levels of the respiratory control system including the central and peripheral chemoreceptors. The most important factors that contribute to this type of breathing are the following.

Immaturity of the Respiratory Control

The Role of the Decreased Activity of the Central Respiratory Chemoreceptors. These receptors, mostly responsible for the hypercapnic ventilatory response, are considered the most important chemoreceptors that modulate breathing and promote regular and continuous respiration. The activity of these chemoreceptors is measured by the ventilatory response to carbon dioxide (CO_2). This response to CO_2 is expressed as the change in minute ventilation with the changes in alveolar CO_2. Preterm infants have a decreased response to CO_2 and therefore increased ventilation is not triggered until higher levels of CO_2 are achieved. This response increases with gestational age and postnatal age likely related to the maturation of the central nervous system. (6)(7)(8)(9) One of the most fascinating findings in preterm infants compared to adults is the opposite response to CO_2 with different concentrations of oxygen. In adults, the lower the concentration of inspired oxygen, the greater is the response to CO_2. On the contrary, in preterm infants, the lower the concentration of inspired oxygen, the more depressed or flat is the response to CO_2 (Fig 3). It is very likely that this paradoxical response is related to the known depressant effect of hypoxia on the central chemoreceptors observed only in premature infants as described later in this article. (6)(7)(8)(9)(10)

The ventilatory response to hypoxia is expressed as the percentage change in minute ventilation with the change in the arterial or alveolar Po_2. This response is also unique in preterm infants and is characterized by a classic biphasic curve with an immediate increase in ventilation lasting 1 to 2 minutes followed by a decrease in ventilation below baseline levels at 5 minutes of hypoxia, often transforming the breathing

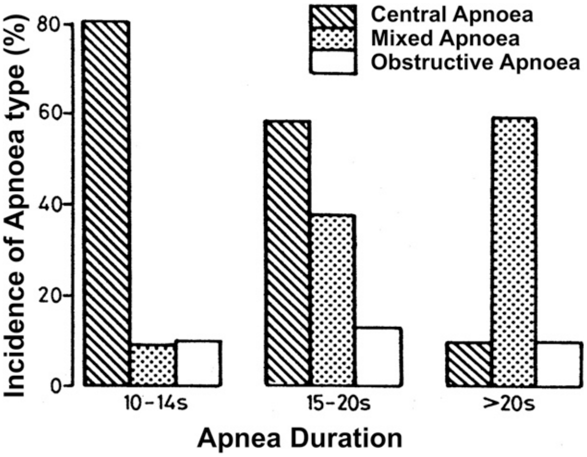

Figure 2. The incidence of different types of apneas according to duration. The proportion of central apneas decreased significantly with increasing duration of apnea ($P<.001$). Conversely, the proportion of mixed apneas increases with the duration of apnea ($P<.001$) (Reprinted with permission from Butcher-Puech MC, Henderson-Smart DJ, Holley D, Lacey JL, Edwards DA. Relation between apnoea duration and type and neurological status of preterm infants. *Arch Dis Child.* 1985;60:953–958.)

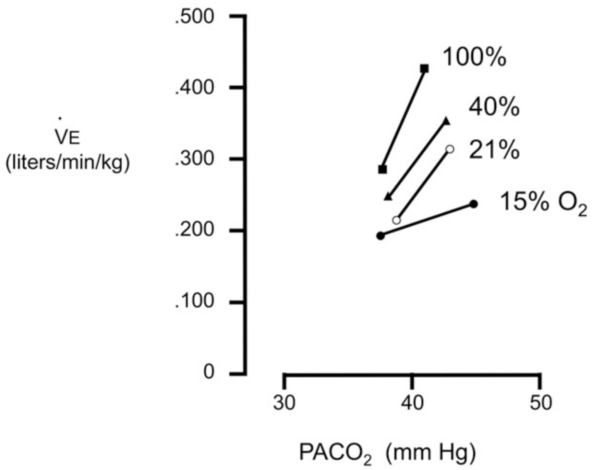

Figure 3. Steady-state carbon dioxide (CO_2) response curves at different inspired oxygen concentrations. The more hypoxic the infant, the flatter was the response to CO_2. (Reprinted with permission from Rigatto H, De La Torre Verduzco R, Gates DB. Effects of O_2 on the ventilatory response to CO2 in preterm infants. *J Appl Physiol.* 1975;39:896–899.)

into irregular and periodic. (7) The immediate increase in ventilation is similar to the one observed in adults and is attributed to the stimulation of peripheral chemoreceptors by hypoxemia. The mechanism responsible for the late ventilator depression is still unclear, but it is likely related to central release of inhibitory neuromodulators in response to hypoxia. (11) Very low-birthweight infants show only a sustained decrease in ventilation in response to inhaled low oxygen (Fig 4). Although the exact relationship between the respiratory depression with hypoxia and neonatal apnea is not fully understood, it is likely a significant factor in the occurrence of periodic breathing and delayed recovery after apnea.

The Role of the Increased Activity of the Peripheral Chemoreceptors. The most important peripheral chemoreceptors that modulate breathing are located in the carotid bodies at the bifurcation of the common carotid arteries. These chemoreceptors respond to rapid decreases in arterial Po_2 and pH and increases in arterial Pco_2 and are mostly responsible for transient changes of these variables. The relationship between the arterial Po_2 and the firing rate of the peripheral chemoreceptors is nonlinear with very little response until the arterial Po_2 is reduced below 100 mm Hg when the rate increases exponentially. Hypoxia promotes respiratory instability by moving the response of these chemoreceptors to the steep part of the curve where small changes in arterial Po_2 and Pco_2 produce large changes in ventilation, leading to unstable respiration. (7)(8)(9) Al-Matary et al showed that the activity of peripheral chemoreceptors is much higher in the newborn than in the adult and in neonates who breathe periodically compared with those who breathe continuously. (12) This increase in the activity of peripheral chemoreceptors is because arterial Po_2 is lower in this group of newborns. These findings support the hypothesis that the drive to breathe early in life depends on increased peripheral chemoreceptor activity, and that this heightened peripheral chemoreceptor activity may play a role in disturbing the respiratory control system, leading to periodic breathing and apnea. The fact that small increases in oxygenation significantly decrease periodic breathing and apnea supports the notion that hypoxemia is a crucial factor in the mechanism responsible for apnea of prematurity.

The Role of the Pco_2 Apneic Threshold. The Pco_2 apneic threshold is the minimal Pco_2 level required to sustain breathing. When the CO_2 decreases below this minimal level, breathing stops. This notion of a CO_2 apneic threshold is crucial to our understanding of periodic breathing and apnea in humans. Recent publications have suggested that the closer the eupneic Pco_2 is to the threshold Pco_2, the more prone the patient is to instability of breathing. (13) Khan et al showed that the average CO_2 apneic threshold in preterm infants is only 1.5 mm Hg lower than the actual or baseline Pco_2, whereas in adults it is ~5 mm Hg lower. (14) This narrow difference between eupneic and apneic Pco_2 in neonates is likely related to a low baseline Pco_2 because of a decrease in metabolism triggered by hypoxemia. Thus, the great variability in tidal volume with major oscillations in Pco_2 under normal circumstances, together with the closeness of the CO_2 apneic threshold to the baseline CO_2, likely contributes to the high prevalence of periodic breathing in infants compared with adults (Fig 5) (6)(7)(8)(9).

Pulmonary Mechanics

The FRC is important to maintain oxygenation and decrease the degree of oxygen desaturation during brief periods of apnea. Preterm infants are particularly prone to an inadequate expiratory lung volume because of their highly compliant chest wall, which lead to closure of the distal airway, potentially leading to intrapulmonary shunting. (15) To compensate for this disadvantage, preterm infants use compensatory mechanisms such as expiratory braking, shortening of expiratory time, and sighing to try to maintain lung volume. These mechanisms are mediated through the inflation and deflation vagal reflexes (Hering-Breuer reflexes).

Activation of intercostal muscles contributes to chest wall stability and maintenance of FRC. However, these muscles are tonically inhibited during rapid eye movement (REM) sleep which is problematic because premature infants spend more than 50% in this sleep state. (6)(11) The disappearance of tone in the intercostal muscles has been suggested as a major factor responsible for the increased

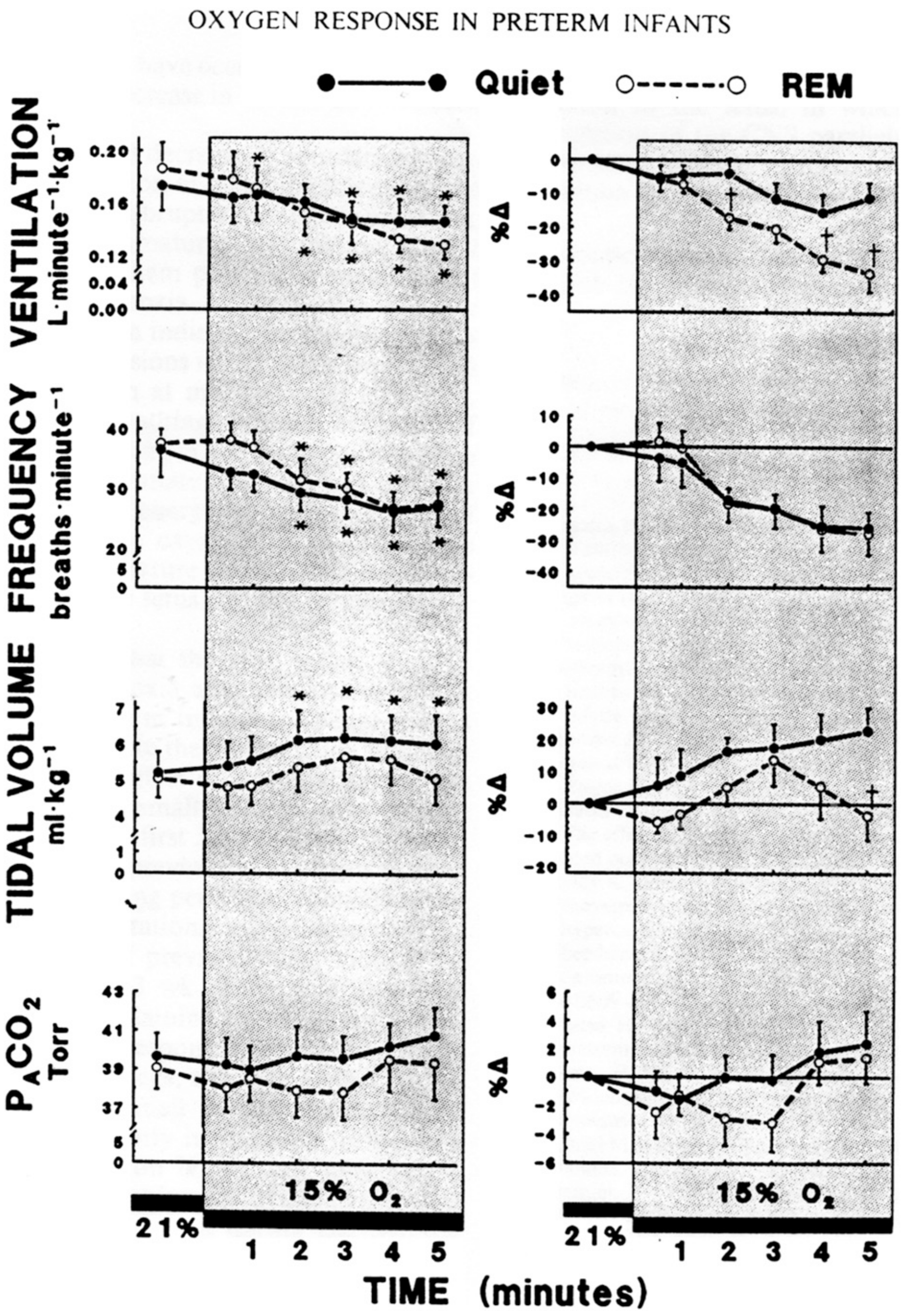

Figure 4. Changes in ventilatory variables in response to 15% oxygen in preterm infants of less than or equal to 1,500 g. Left, sustained decrease in ventilation occurred in both sleep states, mainly due to a decrease in frequency. Right, percentages of change show that ventilation decreased significantly more during REM sleep than in quiet sleep as a result of a lack of increase in tidal volume. Values are mean ± SEM; *, $P \leq .05$ compared with controls; †, $P \leq .05$ between sleep states. (Reprinted with permission from Alvaro R, Alvarez J, Kwiatkowski K, Cates D, Rigatto H. Small preterm infants (less than or equal to 1500 g) have only a sustained decrease in ventilation in response to hypoxia. *Pediatr Res.* 1992;32:403–406.)

chest distortion and chest wall collapse seen on inspiration during REM sleep in infants, which leads to decreased FRC.

Upper Airway and Pulmonary Reflexes

The laryngeal chemoreflexes (LCRs) comprise a group of reflexes triggered by the contact between liquids and receptors of the laryngeal mucosa. Stimulation of the laryngeal mucosa in premature infants, either chemically or mechanically, can lead to apnea, bradycardia, and oxygen desaturation. This reflex-induced apnea is mediated through superior laryngeal nerve afferents. Immature LCRs, characterized by an exaggerated inhibitory cardiorespiratory response, are mainly observed in preterm infants or in conditions in which upper airway inflammation is present.

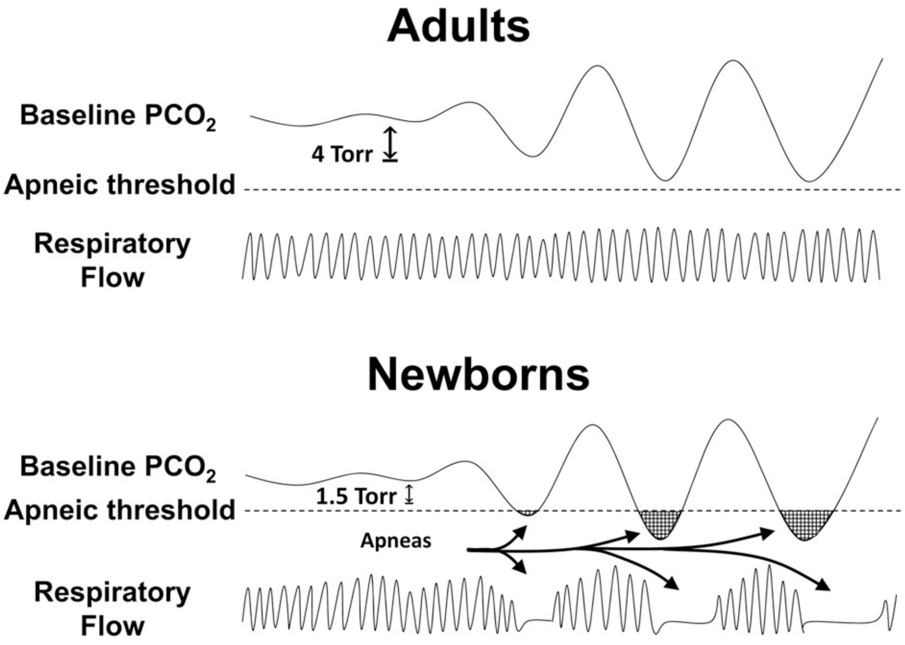

Figure 5. Diagrammatic representation of the relationship between the P_{CO_2} apneic threshold and the baseline or actual P_{CO_2} levels in adults and newborns. Because of the proximity of these 2 levels in newborns, P_{CO_2} is much more likely to drop below the apneic threshold than in adults.

With maturation, the duration and severity of apneas secondary to LCRs decrease. This is in part related to decreased stimulation of the LCR because of improved coordination of upper airway muscles and the increase in the excitatory respiratory-related neurons within the respiratory network that counterbalance the inhibitory afferent input from the LCR.

Inflation of the lungs is associated with a decrease in inspiratory time and prolongation of expiratory time mediated through stimulation of vagal receptors (Hering-Breuer inflation reflex). This reflex is much more active in the newborn period than in adult life when small increases in lung volume can cause apnea. (6)(7)(9)(11) Reduction in lung volume can activate the Hering-Breuer deflation reflex. This reflex shortens expiration and prolongs inspiration. This reflex is less active in premature infants and can cause inhibition of breathing and short apneas when stimulated.

Spontaneous distortion of the thoracic cage, which occurs most commonly in premature infants during REM sleep, may trigger diaphragmatic inhibition through the intercostal inhibitory reflex and may contribute to the onset of periodic breathing and apnea. (6)(7)(9)(11) The immaturity of other reflexes, such as those associated with obstruction of the airway (gamma system), aspiration of endotracheal tube (irritant reflexes), and pulmonary congestion from a significant left to right shunt through the ductus arteriosus (J receptors), could also contribute to some type of apnea in preterm infants.

Sleep State

We now know that sleep modulates breathing and predisposes patients to apnea. We also know that most apneas occur during REM sleep, which is usually accompanied by irregular breathing in terms of the frequency and amplitude of the tidal volume. (6)(11) The effects of sleep on breathing in preterm infants are many. REM sleep increases the incidence of periodic breathing and apnea, decreases the ventilatory response to CO_2, enhances the late decrease in ventilation with hypoxia, increases the rate of sighs, increases chest distortion leading to muscle fatigue and increased oxygen consumption, inhibits pulmonary reflexes, and decreases upper airway tone and postinspiratory activity of the diaphragm leading to partial lung collapse during expiration. (6) These changes will no doubt affect newborns much more because they spend 80% of time sleeping compared with adults who spend only 30% of time sleeping, with a higher percentage of this sleep in the REM state.

Infection and Inflammation

Recent evidence suggests that infection and inflammation may play a crucial role in the pathogenesis of apnea of prematurity. (1)(5) The progressive inflammation observed in the lungs of preterm infants secondary to intra- and extrauterine infection and the oxidative stress caused by oxygen exposure and mechanical ventilation leads to respiratory morbidity. This negative effect of infection and inflammation on respiratory development would contribute to a worsening apnea of prematurity and aggravation of the intermittent chronic hypoxic episodes observed during periodic breathing and apnea. This local and systemic inflammation, in turn, could have short- and long-term effects by increasing the expression of inflammatory mediators in the central and peripheral nervous system, modifying the structure and function of chemoreceptors. This effect on the already immature respiratory neural control system may destabilize breathing and cause apnea and chronic intermittent hypoxemic events. This intermittent hypoxia and its recovery to normoxia or hyperoxia may also increase oxidative stress and predispose the infant to a proinflammatory cascade that may further inhibit central respiratory neural output and aggravate the problem. These chronic intermittent hypoxemic events not only increase respiratory instability, but also alter growth and cardiovascular regulation, and increase the risk for retinopathy of prematurity and neurologic disability. (1)(3)(4)(5)(16)(17)(18)

DIAGNOSIS

The high incidence of apneas in preterm infants makes cardiorespiratory monitoring mandatory in children younger than 35 weeks of gestation and in all high-risk infants. Most neonatal units use a combination of respiratory impedance, heart rate, and pulse oximeter monitors. Although respiratory impedance monitors do not detect obstructive apneas, heart rate and oxygenation monitors generally detect bradycardia and decreased oxygenation associated with such apneas. For the accurate diagnosis of airway obstruction, more sophisticated monitoring such as pneumotacography, nasal thermistors, plethysmography, and CO_2 expiratory pressure monitors are needed but rarely used in daily practice. The sudden increase in the number or severity of apneas in preterm or term infants should be investigated to rule out other clinical problems associated with apneas. Continuous pulse oximetry (SpO_2) measured by new generation high-resolution pulse oximeters with target oxygen ranges is a very important monitoring tool to assess the degree of intermittent hypoxemic events associated with periodic breathing and apnea. Frequent assessment of SpO_2 measurements, including the percentage of time infants spend within their desired target oxygen saturation range and the number of prolonged hypoxemic events could be an important and valuable strategy to adapt and reflect the intensity of therapeutic interventions and improve neonatal outcomes.

TREATMENT

General

The integral management of apneas in preterm infants involves the diagnosis and correction of secondary causes before making a conclusive diagnosis of apnea of prematurity. The decision to start medical treatment should be based not only on the frequency and duration of events but also on the severity of the apnea measured by the degree of bradycardia, hypoxemia, and the intensity of the stimulation necessary to end the apnea. In general, the lower the gestational age, the more aggressive the treatment should be.

In very low-birthweight infants, the temperature should be maintained at the minimum level of the neutral thermal environment (97.7°F–98.2°F [36.5°C–36.8°C]). Although the ideal position to reduce apneas is somewhat controversial, in this author's institution, the prone position is recommended, with the head-elevated tilt position about 30 to 45 degrees in a nestlike environment. This would improve lung function by stabilizing the chest wall and respiration, facilitating thermoregulation, reducing gastroesophageal reflux, and stabilizing the autonomic nervous system. (1)(2)(9)(10)(11)(18)(19) Although no studies have been conducted to evaluate the benefits or damage of increased inhaled oxygen concentration, it is important to keep these premature infants well oxygenated, avoiding hyperoxemia. At this author's institution, oxygen saturation is maintained between 88% and 92%. Higher range (90%–94%) may be considered in infants of more than 32 weeks' postmenstrual age with frequent episodes of intermittent desaturation.

Medical

Methylxanthines. Since the first report in by Kuzemko and Paala in 1973, several studies have confirmed the efficacy of methylxanthines in decreasing the frequency of apneas and the use of mechanical ventilation in preterm infants. (20) The main mechanism of action of methylxanthines is through a competitive antagonism of adenosine, a potent inhibitor of respiration. Methylxanthines increase ventilation, improve CO_2 sensitivity, decrease hypoxic depression, and increase diaphragmatic activity. (1)(2)(9)(10)(11)(17)(19)(21) The undesirable effects of xanthines include tachycardia, cardiac arrhythmias, feeding intolerance, increased basal metabolism and oxygen consumption, irritability, and much less frequently, convulsions.

The most commonly used xanthines are theophylline and caffeine. Although the efficacy is similar, caffeine citrate is preferred because of its longer half-life, greater therapeutic margin, fewer undesirable effects, fewer daily doses, and a lack of need for plasma level control. The largest study of caffeine in preterm infants of less than 1,250 g showed that caffeine not only decreases the incidence of bronchopulmonary dysplasia, but also increases survival without neurologic disability. (22)(23) This study used a loading dose of 20 mg/kg of caffeine citrate followed by maintenance doses of 5 to 10 mg/kg per day. Caffeine can be administered intravenously or orally and the dosage is similar for both. In the case of theophylline, the loading dose is 5 to 6 mg/kg per day, with a maintenance dose of about 2 to 4 mg/kg per day divided every 8 to 12 hours depending on the gestational age. Although the optimal time to start caffeine in patients at risk for apnea is not known, it is recommended to start as soon as possible in patients of less than 28 weeks' gestational age especially if they are receiving mechanical ventilation. Because of the prolonged half-life, the patient should be observed for a period of no less than 5 to 7 days after cessation of caffeine and before discharge. A recent randomized controlled study showed that the use of caffeine in small preterm infants after 34 weeks' postconceptional age decreases the frequency and intensity of intermittent hypoxic episodes. (24)

Nasal Continuous Positive Airway Pressure. Nasal continuous positive airway pressure (CPAP) used in conjunction with xanthines has been shown to be very effective in reducing the frequency and severity of apnea of prematurity. The most important effects are related to improvement in lung volume and FRC and consequently in oxygenation. Nasal CPAP mainly decreases mixed and obstructive apneas by keeping the airway open and stabilizing the thoracic cage. (1)(2)(9)(10)(11)(17)(19)(21) Low pressures of 4 to 6 cm H_2O are generally effective in suppressing apneas. Pressures greater than 6 cm H_2O are more effective only in cases of residual pulmonary disease or in cases of laryngotracheomalacia. In young preterm infants, high levels of pressure may increase work of breathing and lead to muscle fatigue.

Recent technologic advances have allowed the synchronized or nonsynchronized use of nasal intermittent positive pressure ventilation (NIPPV), and nasal CPAP with variable flow. NIPPV would decrease the closure of the upper airway and stimulate the respiratory center through an intermittent increase in pressure at the pharyngeal level. (2)(17)(19) Several randomized trials are under way to test the effectiveness and safety of these new techniques for the treatment of apnea of prematurity. The use of high-flow nasal cannula therapy is increasingly used as a convenient, more portable alternative to CPAP delivery devices. Some questions remain about the safety and efficacy of devices that provide relatively unregulated high flow as a means of CPAP delivery.

Mechanical Ventilation. When severe apnea persists despite the aforementioned treatments, intubation and mechanical ventilation are the last resort. Minimal ventilation parameters should be used, which allow spontaneous breathing and minimize the risk for lung damage. At this author's institution, the use of assisted control volume guaranteed ventilators is preferred, which have short inspiratory times and a level of positive end-expiratory pressure according to pulmonary pathology. The duration of mechanical ventilation depends on the cause of the apneas but in general it is for short periods.

Treatments not Recommended or not Properly Studied

Although gastroesophageal reflux is able to produce apnea through stimulation of laryngeal chemoreceptors, several studies have clearly demonstrated that treatment for gastroesophageal reflux with antacids or gastrointestinal motile stimulants are not only ineffective for the treatment of apnea of prematurity but also could be associated with important undesirable effects such as necrotizing enterocolitis, sepsis, and death. (1)(2)(17)(19) Several studies have shown that doxapram, used in continuous intravenous infusion, may decrease the incidence of refractory apneas to xanthines and the need for intubation. Their action would be mediated through the stimulation of central and peripheral chemoreceptors. Because of the limited number of studies and the level of evidence, coupled with its important side effects such as seizures, arterial hypertension, arrhythmias, gastrointestinal disorders, and a possible worse neurologic development in the long term, doxapram is not currently recommended for the treatment of apnea of prematurity. Mechanosensory stimulation using acoustic mattresses may reduce the incidence of apnea and oxygen desaturation. More studies are needed to corroborate its use at the clinical level. The effect of blood transfusions on apnea of prematurity is controversial. Although recent studies have shown an improvement in the number of apneas after transfusion, the effect is minimal and transient. Currently, there is no information to suggest that blood transfusion offers long-term benefits (1)(2)(17)(19)

SUMMARY

Apnea is one of the most important clinical problems in NICU, especially nowadays when smaller preterm infants survive and undergo extubation early with the use of surfactant. Most apneas are idiopathic and represent a physiologic manifestation of an unstable breathing pattern that reflects the immaturity of the control of breathing and adaptation to extrauterine life that improves with gestational age. The low level of oxygenation in preterm infants leads to inhibition of central chemoreceptor activity, increased activity of peripheral chemoreceptors, and a narrow difference between the eupneic and apneic CO_2 that predisposes infants to periodic breathing and apnea. Chronic episodes of intermittent hypoxia associated with these apneas and periodic breathing may further increase the expression of inflammatory mediators in the central nervous system. This effect produces increased respiratory instability and also altered growth and cardiovascular regulation, and increases the risks of retinopathy of prematurity and neurologic disability. Medical treatment with respiratory stimulants and the use of nasal CPAP are generally effective and should always be combined with an optimal general supportive treatment.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the pathophysiology of apnea of prematurity.
- Know the management of apnea of prematurity.

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1. A 26-week gestational age infant is now 3 weeks old in the NICU and is having occasional episodes of apnea and bradycardia. Immaturity of respiratory control plays an important role in the pathogenesis of apnea of prematurity. Which of the following statements regarding control of breathing in preterm infants is true?
   - A. Unlike in adults, hypoxia results in an immediate decrease in ventilation characterized by irregular and periodic breathing.
   - B. Peripheral respiratory chemoreceptors are considered the most important chemoreceptors that modulate breathing and promote regular and continuous respiration.
   - C. The lower the concentration of inspired oxygen, the greater is the response to carbon dioxide (CO_2).
   - D. Preterm infants have a decreased response to CO_2 and therefore increased ventilation is not triggered until the levels of CO_2 are higher.
   - E. Peripheral chemoreceptors respond to rapid increases in arterial Po_2 and pH and decreases in arterial Pco_2.
2. A 24-week gestational age infant is now 2 weeks old and receiving maintenance nasal continuous positive airway pressure. The infant is noted to have intermittent work of breathing with retractions. Preterm infants are prone to inadequate expiratory lung volumes because of their highly compliant chest wall. Which of the following mechanisms is inhibited during rapid eye movement (REM) sleep and may contribute to chest wall collapse during REM sleep in preterm infants?
   - A. Expiratory braking.
   - B. Shortening of expiratory time.
   - C. Intermittent sighs.
   - D. Activation of intercostal muscles.
   - E. Decrease in effective time constant.
3. A 26-week gestational age male infant has been transitioned to respiratory support by nasal cannula oxygen. He has intermittent episodes of apnea and bradycardia. These episodes typically resolve spontaneously, but occasionally require stimulation or increased oxygen. It is recognized that upper airway and pulmonary reflexes play an important role in the pathophysiology of apnea of prematurity. Which of the following statements regarding these reflexes is correct?
   - A. lack of stimulation of the laryngeal chemoreflexes (LCRs), either chemically or mechanically, leads to apnea, bradycardia, and oxygen desaturation in preterm infants.
   - B. Immature LCRs are characterized by a lack of inhibitory cardiorespiratory responses.
   - C. The Hering-Breuer inflation reflex is a unique feature of preterm physiology and is triggered by apnea and bradycardia, leading to lung collapse.
   - D. Reduction in lung volume can activate the Hering-Breuer deflation reflex, which shortens expiration and prolongs inspiration. This reflex is less active in premature infants.
   - E. Distortion of the thoracic cage, which occurs most commonly in premature infants during awake activity, triggers cycles of tachypnea and apnea through the intercostal inhibitory reflex.
4. An infant born at 25 weeks' gestational age is now at a corrected age of 28 weeks, and is in the NICU receiving continuous monitoring. She is noted to have apneic episodes, particularly during sleep. Sleep has been shown to modulate breathing and predispose premature infants to apnea, with most apnea events occurring during REM sleep. Which of the following statements regarding the effects of REM sleep on apnea is correct?

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A. REM sleep is associated with a heightened state of pulmonary reflexes.
B. REM sleep decreases the incidence of periodic breathing.
C. REM sleep decreases the ventilatory response to CO_2.
D. REM sleep increases upper airway tone and postinspiratory activity of the diaphragm.
E. REM sleep inhibits the late decrease in ventilation with hypoxia.

5. An infant born at 24 weeks' gestational age has been receiving mechanical ventilation since admission to the NICU, and is now 1 week old and ready to transition to noninvasive ventilation. You are considering strategies to manage apnea of prematurity. Which of the following statements regarding management of apnea of prematurity for preterm infants is correct?

A. Methylxanthines decrease apnea frequency through a competitive antagonism of nitric oxide synthase.
B. Theophylline has similar efficacy as caffeine, but is less commonly used because of its narrower therapeutic margin and its need for plasma level control.
C. Nasal continuous positive airway pressure is often used in apnea of prematurity, but has not been shown to reduce the frequency or severity of apneas in infants born before 28 weeks' gestational age.
D. Meta-analyses have shown that antacid and promotility agents are effective for the treatment of apnea of prematurity, with low risk of short- and long-term adverse events, and with excellent cost-benefit value.
E. Regardless of hematocrit value, blood transfusions are effective in decreasing frequency of apnea in the short-term and improving neurodevelopmental outcomes at 2 years of age.

Control of Breathing and Apnea of Prematurity

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NeoReviews 2018;19;e224
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Screening with Pulse Oximetry for Early Detection of Neonatal Hypoxemia

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Objectives After completing this article, readers should be able to:

1. Apply early pulse oximetry newborn screening to identify diseases associated with neonatal hypoxemia.
2. Identify differences in screening protocols and algorithms.
3. Describe the impact of early detection of critical congenital heart defects and hypoxemic neonatal conditions.

Abstract

Neonatal hypoxemia is sometimes difficult to detect. Therefore, it is sometimes challenging to diagnose critical congenital heart defects and other hypoxemic conditions before the infant becomes seriously ill. Screening with pulse oximetry is a noninvasive and inexpensive valuable method for early detection of these conditions. Establishing a protocol for all newborns saves lives and decreases morbidity without increasing costs.

Education Gaps

1. Normal neonatal saturation values in room air at sea level and at high altitude varies after the period of transition from fetal to neonatal life and up to 48 hours of age.
2. Cyanosis is not a very reliable clinical sign to detect neonatal hypoxemia.
3. Technology is available for evaluation and screening of neonatal hypoxemia.

AUTHOR DISCLOSURE Dr Sola has disclosed that he is a part-time member of the Masimo (Irvine, CA) speakers' bureau. Dr Golombek has disclosed that he is on the speakers' bureau of Mallinckrodt and a consultant with Prolacta. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
CCHD	critical congenital heart defects
PI	perfusion index
PPHN	persistent pulmonary hypertension
SET	signal extraction technology
SIBEN	Ibero-American Society of Neonatology
Spo_2	pulse oximetry

INTRODUCTION

Congenital heart disease is one of the most common types of birth defects, affecting approximately 8 in 1,000 live-born infants. Critical congenital heart defects (CCHD), including ductal-dependent lesions, occur in 1 to 3 per 1,000 live births, and account for about 40% of deaths associated with congenital malformations occurring in the first year of age. It is estimated that 60% of neonatal deaths in the United States are preventable. Neonatal hypoxemia is potentially fatal if there is a delayed or missed diagnosis of CCHD, pneumonia, sepsis, or persistent pulmonary hypertension (PPHN). Earlier detection of these pathologic conditions leads to improved management and outcomes. Numerous references support these statements but, for the purposes of providing an overview, we have limited the number cited in this review.

The prevalence, epidemiology, and impact of delay in the diagnosis of hypoxemic newborn diseases have been described in several publications. (1)(2)(3)(4)(5)(6)(7)(8) More than 30% of infant deaths associated with CCHD have been attributed to a late or missed diagnosis, which raises a concern for neonatal safety. (6) In Great Britain, it was estimated that 25% of infants with CCHD were not diagnosed until after discharge from the hospital when the infant presented in critical condition. (9)(10)(11)(12) In developing countries, it is estimated that more than half of neonates with CCHD are diagnosed after the first week of age. (13)(14)(15) It is now understood that routine prenatal imaging or physical examination of the neonate is insufficient for the early neonatal detection of potentially lethal cardiac conditions and that the delay in diagnosis may increase the risk of death or permanent injury.

This concern about delayed diagnosis of CCHD led to exploring the value of early detection with pulse oximetry (Spo_2) monitoring. Spo_2 is a noninvasive method that allows for rapid measurement of saturation of hemoglobin in arterial blood. It can detect hypoxemia in asymptomatic newborns with severe health conditions. Pulse oximetry with signal extraction technology (SET) is very easy to perform, fast, noninvasive, and cost-effective, and has significantly improved the quality and safety of neonatal health care. There is currently sufficient evidence on the benefits of Spo_2 CCHD screening, and many organizations such as the US Advisory Committee on Hereditary Diseases endorse this screening test. (16)(17)(18)(19)(20) In 2015, the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) convened an interdisciplinary panel with the goal of learning about practices in the United States that diagnose CCHD and identify opportunities for improvements. Many of their recommendations were published in April 2016 and are included in this review. (15)

A fetal anatomic survey with ultrasonography can identify cardiac structural abnormalities; however, this detailed ultrasonographic method is operator-dependent and highly inconsistent. Prenatal detection of CCHD is highly variable. (21) In 1 recent report of more than 30,000 fetuses from Norway, only 57% of affected fetuses were identified prenatally. (22) In some cases, the diagnosis of fetal CCHD is inaccurate, with postnatal studies showing a different cardiac defect or a structurally normal heart. Prenatal care and assessment is also highly variable in different countries and repeated prenatal ultrasonography is impractical and costly.

In 2009, de-Wahl Granelli et al published a cohort study of 39,821 newborns, which showed the impact of measuring oxygen saturation with Spo_2 in the upper and lower extremities. (23) This group used a monitor that properly measured Spo_2 despite motion and low perfusion. Ewer et al confirmed the importance of using the same technology for early detection of CCHD in 20,055 asymptomatic newborns; their study showed the accuracy of this screening, even during the first few hours after birth. (24) Zhao and colleagues in China studied 100,000 newborns and demonstrated the same benefit. (25) In January 2012, the AAP published recommendations, with the approval of the US Department of Health, to perform oximetry to evaluate all newborns for CCHD. (16)(17)(18) In addition to CCHD, several other serious hypoxemic conditions can be diagnosed early with Spo_2 screening.

This article will review the recommendations for early Spo_2 newborn screening to identify diseases associated with neonatal hypoxemia. The information is obtained from all the cited references and also from the IX Clinical Consensus of the Ibero-American Society of Neonatology (SIBEN). (15)(26) At SIBEN's Annual 2016 Congress in Asunción, Paraguay, 39 neonatologists and 4 neonatal nurses from 18 Ibero-American countries met and published the recommendations listed herein.

The early evaluation of all newborns with Spo_2 screening is a noninvasive, easy to perform, and low-cost method that can be performed between 8 and 48 hours of age. It has excellent clinical utility at detecting potentially serious diseases in asymptomatic infants. The universal implementation of this evaluation in clinical practice enhances cardiopulmonary assessment, increases patient safety, and reduces morbidity, sequelae, and mortality.

WHAT ARE THE NEONATAL CONDITIONS FOR WHICH DETECTION OF HYPOXEMIA WITH Spo_2 CAN BE USEFUL BEFORE SEVERE CLINICAL MANIFESTATIONS OCCUR?

The Spo_2 screening test is very useful for the early detection of neonatal conditions with hypoxemia. The specific cardiac defects that can be detected and which require intervention (ie, catheterization or surgery) during the first year of age are listed in Table 1.

It is important to recognize that, in addition to congenital heart disease, the following conditions can be identified with

TABLE 1. **Critical Heart Lesions Detected on Pulse Oximetry Screening**

LEFT-SIDED LESIONS	*RIGHT-SIDED LESIONS*
Hypoplastic left heart syndrome	Pulmonary atresia (intact septum or with a ventricular septal defect)
Interruption of the aortic arch	Pulmonary valve stenosis
Coarctation of the aorta, severe	Tricuspid atresia
Aortic valve stenosis	Ebstein anomaly Tetralogy of Fallot Transposition of the great vessels Anomalous pulmonary venous return Truncus arteriosus

Spo$_2$ screening: 1) early sepsis, 2) congenital pneumonia, 3) PPHN, 4) meconium aspiration, 5) transient tachypnea of the newborn, 6) pneumothorax, and 7) other less frequent varied neonatal conditions.

This method of screening is not a reliable indicator of obstruction of the airway (eg, choanal atresia, dysfunction of the vocal cords) because these airway lesions may be associated with alveolar hypoventilation, with an elevated Paco$_2$ but normal Pao$_2$. However, if these newborns are hypoxemic, the Spo$_2$ screening will also be abnormal.

HOW SHOULD EARLY Spo$_2$ SCREENING BE PERFORMED?

General Clinical Protocols

Neonatal screening for the detection of pathologic conditions with hypoxemia has been used in clinical practice since 2011. Since then, studies and meta-analyses have shown that such screening meets the criteria for a population screening test.

The Spo$_2$ screening is an easy technique, and should be performed in all apparently healthy newborns between 12 and 48 hours after birth or before discharge. (Note: the timing of the screening varies among protocols.) The clinician can perform this screen by placing 1 sensor in the palm of the newborn's right hand (preductal) and another sensor on 1 of the newborn's feet (postductal). For preductal measurements, all large investigations have placed the sensors on the palm and the US Food and Drug Administration has recommended palm placement when using pulse oximetry monitors. Although the left hand may be used for a preductal measurement, it is not the preferred site because it only reflects the preductal value 80% of the time. These 2 Spo$_2$ readings can be obtained consecutively with 1 monitor or simultaneously with 2 monitors.

Pre- and Postductal Spo$_2$ Differences

Spo$_2$ screening requires both preductal and postductal measurements to avoid an increase in false-negative and false-positive results. Newborns with obstruction of the left outflow tract may not be diagnosed if a single-site measurement is used. Ewer (12) and de-Wahl Granelli et al (27) also observed that both measurements increase the chances of early diagnosis of other serious hypoxemic conditions in the neonate.

In healthy newborns without heart disease, the normal Spo$_2$ value is usually greater than 94% in both locations and the difference between the preductal and postductal measurements is minimal. In 1 study, oxygen saturations were measured in 13,714 healthy newborns without cardiac or pulmonary disease at a median age of 25 hours using Spo$_2$ monitors with SET, and with 8- to 10-second mean times and reusable probes. The preductal or postductal Spo$_2$ was greater than or equal to 95% in 99.5% of the infants, with the mean postductal Spo$_2$ value being higher than the preductal Spo$_2$. (28) In 40% of these infants, the postductal Spo$_2$ value was higher than the preductal Spo$_2$, with 38% having equal pre- and postductal Spo$_2$ values and 22% with postductal Spo$_2$ values that were lower than the preductal Spo$_2$. However, any difference was clinically insignificant, with a mean difference of only 0.29%.

The definition of a significant difference between pre- and postductal Spo$_2$ during screening varies based on the protocol chosen for screening. The recommendations endorsed by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children of the USA, (16) which are based on the protocol of de-Wahl Granelli et al (23) consider a difference of more than 3% to be significant. However, in the UK protocol, which is based on the studies of Ewer et al, a difference of more than 2% was considered to be significant. (24) These differences are significant regardless of whether the preductal Spo$_2$ value is higher than the postductal Spo$_2$ value or vice versa and even if both preductal and postductal Spo$_2$ measurements are normal (ie, >95%).

The differences in Spo$_2$ measurements can occur with: 1) a normal Spo$_2$ (>95%) in both the right hand and 1 foot; 2) an abnormal Spo$_2$ (<95%) in both extremities; and 3) an abnormal Spo$_2$ in 1 territory (ie, preductal or postductal) but normal in the other territory.

When the preductal Spo$_2$ value is higher than the postductal Spo$_2$ value, possible explanations include 1) obstructions to the left heart with a right-to-left ductal shunt, and 2) persistent PPHN of the newborn with a right-to-left ductal shunt.

When the postductal Spo$_2$ value is higher than the preductal Spo$_2$ value, possible reasons are 1) an error in the monitor, or 2) transposition of the great vessels with a conotruncal abnormality (eg, obstruction due to aortic stenosis or an interrupted aortic arch).

In summary, a significant difference between pre- and postductal values (>2% or >3%) indicates the presence of a shunt at the ductal level, and points to an abnormality, regardless of which of the 2 territories is higher. Of course, there are abnormal cardiac conditions without a pre-/postductal Spo_2 difference; this occurs when the blood mixture of deoxygenated and oxygenated blood (ie, "shunt") occurs mostly at other levels (eg, anomalous venous return, atrial level, ventricular level) and there is very little or no shunt at the ductal level. However, in these cases, the Spo_2 is usually less than 95%.

Technology for Screening

For accurate Spo_2 screening, it is important to use equipment that provides reliable results during motion and in low perfusion situations; in addition, the technique should show the pulsed wave signal and the perfusion index (described later). de-Wahl Granelli et al, Ewer et al, and Zhao et al showed that about 200,000 nurses (23)(24)(25) were able to perform Spo_2 screening using this technology without difficulty. Interestingly, 1 study found that Spo_2 screening did not improve CCHD detection in 15,299 newborns (29); however, the monitor used in this study did not have the appropriate technology to obtain stable signals, which may explain the negative results of this study.

Evaluating the quality of the Spo_2 signal is fundamental to correctly interpret the Spo_2 reading; therefore, Spo_2 screening should be performed with a monitor that is not altered by movements or affected by low perfusion.

Interpretation of Spo_2 Screening

The cumulative published experience to date may be insufficient to draw conclusions about the ideal Spo_2 screening.

The 2 protocols previously mentioned agree in defining the screen as abnormal or "fail" if either the preductal or postductal Spo_2 value is less than 90%. (24)(27) This result would require prompt clinical evaluation by a pediatric provider and transfer to a NICU. However, the protocols differ in several areas: age at the time of screening; whether 1 or both territories need to be abnormal (defined as an Spo_2 value of 90%–94%); the cutoff value that defines a significant pre-/postductal Spo_2 difference (>2% or >3%); and the number of times (once or twice) that an abnormal test should be repeated in a healthy-appearing infant. Each of these parameters is discussed below.

Age. The variability of published false-positive rates is mostly related to the age at screening. Studies quoted in the list of references found that the false-positive rate is 0.035% when the screening is done after 24 hours of age compared with 0.9% in screenings performed at 4 to 6 hours of age and 0.09% for screenings done at about 24 hours of age. However, if the screening is planned for 24 hours of age or later, some infants may become acutely ill before the screening and the opportunity for early diagnosis is missed. The current evidence seems to favor screening at about 12 hours of age or, at the latest, by 12 to 24 hours of age.

One or Both Territories. The US recommendation states that *both* territories need to have an Spo_2 reading of 90% to 94% to be considered a "fail" result. Thus, a "pass" or negative screening result could occur if only 1 territory has an Spo_2 level of greater than or equal to 95%. The UK protocol, on the other hand, considers the screen abnormal if *either* the hand or the foot has an Spo_2 reading of 90% to 94% and, therefore, a "pass" is designated only when both territories have an Spo_2 value greater than or equal to 95%.

Difference Between Pre- and Postductal Values. As mentioned before, there are different views about the definition of an abnormal (ie, "fail") Spo_2 screening result. The pre-/postductal Spo_2 difference of greater than 2% is favored by some authors. If this difference persists in 2 evaluations, the infant should be assessed.

Repeating an Abnormal Screen Once or Twice. Some clinicians firmly believe that if the Spo_2 screening is abnormal on 2 assessments, it is not appropriate to wait and repeat a third screening test (as recommended by the US protocol) in an asymptomatic newborn.

With the aforementioned caveats, the Fig summarizes 1 approach to CCHD screening in an asymptomatic newborn, which is as performed in the UK based on the studies of Ewer et al. (9)(10)(11)(12)(24) An infant with any symptoms for cardiac, pulmonary, or infectious disease should be treated as usual, without delays, regardless of the Spo_2 screening result.

This protocol is based on the UK recommendations. If the Spo_2 is greater than or equal to 95% *and* there is a greater than 2% difference, this would fit into the middle scenario and the test should be repeated. The US protocol defines an abnormal result if the pre-/postductal Spo_2 difference is greater than 3%. The US protocol also considers that it is not necessary for both pre- and postductal values to be greater than or equal to 95%; if only 1 of the Spo_2 values is greater than or equal to 95%, the infant 'passes' the screen. Also, the US protocol considers that for an asymptomatic infant to fail the screening evaluation, 3 test results need to be abnormal and therefore the test needs to be repeated a 3rd time.

Preductal values are obtained from the right hand in all screening protocols.

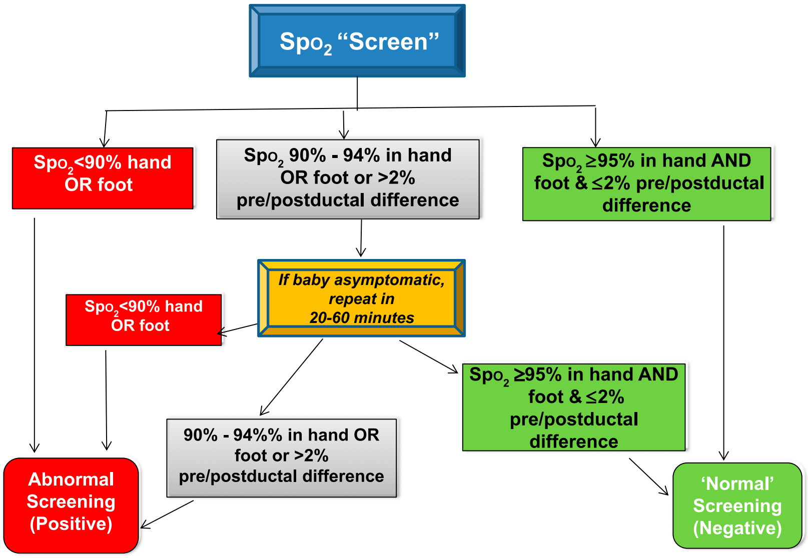
Spo$_2$ "Screen"
Spo$_2$<90% hand OR foot
Spo$_2$ 90% - 94% in hand OR foot or >2% pre/postductal difference
Spo$_2$ ≥95% in hand AND foot & ≤2% pre/postductal difference
If baby asymptomatic, repeat in 20-60 minutes
Spo$_2$<90% hand OR foot
Spo$_2$ ≥95% in hand AND foot & ≤2% pre/postductal difference
90% - 94%% in hand OR foot or >2% pre/postductal difference
Abnormal Screening (Positive)
'Normal' Screening (Negative)

Figure. Protocol for screening an asymptomatic newborn at 12 to 24 hours of age or before discharge.

HOW SHOULD WE RESPOND TO AN ABNORMAL (POSITIVE) SPO$_2$ SCREENING IN A CLINICALLY WELL NEWBORN?

The answer to this question is: *Do not ignore an abnormal test and humbly accept that we may be wrong in our clinical assessment*. After an abnormal result, clinicians need to quickly evaluate the newborn with a detailed and complete examination. Absence of a murmur, the presence of normal femoral pulses, or normal blood pressures does not rule out CCHD. In addition, neonates with hypoxemia from noncardiac conditions may not have a murmur and the other parameters may initially be normal. Unfortunately, there are legal cases in the United States in which a positive ("fail") test result was "ignored," and the infant later became critically ill or died.

It is neither essential nor necessary to perform echocardiography in all infants with a "failed" screening Spo$_2$ test. In addition to careful observation, monitoring, and a detailed physical examination, other studies may be needed to ensure a timely and accurate diagnosis. A complete diagnostic approach may include blood cell counts, cultures, a blood gas, and chest radiography. Some newborns will require echocardiography, and in some, it may be necessary to immediately start an infusion of prostaglandin to maintain patency of the ductus arteriosus (even before echocardiography).

HOW DOES HIGH ALTITUDE INFLUENCE THE RESULTS AND INTERPRETATION OF SPO$_2$ SCREENING?

Data are insufficient to clearly define generalizable normal Spo$_2$ levels within the first 24 hours after birth for the 7% of infants around the world who are born at altitudes higher than 1,500 m (~4921 ft) above sea level. However, understanding cardiopulmonary physiology during fetal life and the transition to extrauterine life, as well as the alveolar gas equation, can assist with establishing the best approach to these infants.

At the SIBEN clinical consensus meeting, (26) clinicians reported that, on average, Spo$_2$ values are not different in the first 12 to 24 hours of age in infants born in locations less than 2,500 m (~8,200 ft) above sea level. In a recent study, Spo$_2$ was measured in newborns at 1,800 m (~5,905 ft) above sea level using a non–motion-resistant Spo$_2$ monitor, which has not been validated in neonates. (30) The 5% and 95% range for Spo$_2$ values reported in this study were about 90% and 98%, with mean and median preductal and postductal Spo$_2$ values only slightly lower than those reported at sea level. The SIBEN consensus statement and others consider that at less than 2,500 m (~8,200 ft) above sea level, the same values as reported at sea level should continue to be used until different well-established evidence becomes available.

At the recommended postnatal age for screening, the *mean* normal Spo$_2$ value is lower at high altitudes (93%–96%), but with larger standard deviations. Therefore, if screening is performed as recommended herein, the values for positive and negative results for each asymptomatic infant could be the same as the values at sea level, bearing in mind that some newborns who are completely healthy can have an Spo$_2$ value of 91% to 94% at altitudes of more than 2,700 m (~8,858 ft) above sea level. For these infants, more detailed observation would be recommended, exercising caution and avoiding aggressive investigations to prevent an increase in the number of "false-positives." Nevertheless, precise cutoff points for Spo_2 values in moderate and high altitudes are not known to adequately balance sensitivity with false-positive rates.

FALSE-POSITIVE AND FALSE-NEGATIVE SCREENING

As mentioned, an infant with a positive screening test has 1 Spo_2 value less than 90% or 2 consecutive Spo_2 values of 90% to 94% and/or a pre-/postductal difference greater than 2%, based on the UK protocol. A false-positive result occurs when additional testing after a positive screen finds that the infant does NOT have any hypoxemic condition such as CCHD, PPHN, transient tachypnea of the newborn, sepsis, or meconium aspiration. This false-positive occurrence is extremely rare (<0.1%) if the screening method and protocol are followed rigorously. If Spo_2 screening is performed before 12 hours of age, the false-positive rate is slightly higher but the diagnosis of infectious and respiratory causes of hypoxemia are obtained earlier.

A false-negative result occurs when the Spo_2 value is normal (negative screening) but the infant is actually found hours or days later to have a hypoxemic condition. Most studies indicate that the most frequently undiagnosed lesions are left-sided obstructed lesions with obstruction to the outflow of the aorta (eg, coarctation of the aortic arch, hypoplastic left heart, aortic stenosis), which are not necessarily associated with hypoxemia. False-negative results can also occur if the technology is inadequate. The use of the preductal and postductal saturations, as described before, and the perfusion index, described later, can be of some value to improve detection but they are not infallible.

HOW SHOULD WE CARE FOR THE FAMILY OF A NEWBORN WITH AN ABNORMAL OR POSITIVE SCREENING RESULT?

In the first hours after birth, various events generate great emotional tension. Health care professional should make an effort to decrease this by all possible means. Families should always actively participate in the care of their newborn and they should also understand the rationale and specifics of Spo_2 screening.

Studies have shown that parents who are well informed are mostly satisfied with Spo_2 screening tests and perceive screening to be a valuable method to identify sick newborns. In addition, parents of neonates who had a false-positive result did not show greater anxiety than those with negative or normal screening results.

It is recommended that parents receive written information about the Spo_2 screening test. This written information must be accompanied by clear verbal communication and clarification of any questions. If possible, the screening should be performed with the parents present. If the newborn passes the test, there will be no issue. However, if the result is abnormal, parents may be shocked to receive this information. As parents' emotions change from joy to worry, they may not be able to concentrate on the information that is being discussed with them.

All members of the neonatal team (social workers, nurses, nurse practitioners, and physicians) should be trained to empathetically support parents of infants who test positive on Spo_2 screening. If the infant appears to be completely healthy but the Spo_2 screening result is abnormal, clinicians should discuss with the parents the possibility that this is a false-positive result.

Depending on the clinical situation, there may be a need to proceed more or less quickly, but any communication with families should occur in a calm and supportive way. It is imperative to avoid delays while parents are processing the information. Parental uncertainty while waiting for repeat testing or further investigations can alter the relationship of the parents with the infant, and disrupt breastfeeding and maternal recovery. It is therefore especially important that staff members performing these screening tests are prepared in advance about how to communicate and empathize with parents if the results are abnormal.

PERFUSION INDEX

Most studies report that the lesions most often missed on Spo_2 screening are those causing obstruction to aortic outflow (eg, hypoplastic left heart syndrome, critical aortic stenosis coarctation, interrupted arch), which may not necessarily be detected with antenatal ultrasonography, physical examination, or abnormal Spo_2 values. However, an additional SET pulse oximetry measurement may increase detection of CCHD caused by an obstruction to aortic outflow. This measurement is called the perfusion index (PI), which is an assessment of strength of perfusion at the monitored site. A reference value was described for 10,000 newborns with a median value of 1.70% and a fifth percentile of 0.70%. (31) Granelli and Ostman-Smith showed that the addition of an abnormal PI to Spo_2 screening increases the sensitivity of identifying CCHD with an obstruction to aortic outflow. (32) However, adding the PI to the screening criteria may also result in an increase in false-positive results.

The PI is normally higher than 0.70% in both preductal and postductal territories. If it is less than 0.70% in 1 territory, the test should be repeated. After 3 abnormal results in a healthy infant, further evaluation is needed. When the PI is less than 0.45%, it is indicative of low perfusion, which could be due to the aforementioned lesions. If the PI is higher in the postductal territory, it could be due to hypoplastic left heart syndrome or critical aortic stenosis with right-to-left ductal shunting. In this case, the postductal Spo_2 value will also be significantly lower than the preductal Spo_2 value. On the other hand, if the preductal PI is higher than the postductal value, one must consider a diagnosis of interruption of the aortic arch or coarctation of the aorta. More studies are still needed, but a published review summarizes all aspects of the PI in neonates (32) and a recent publication shows that combining PI with Spo_2 screening in nontertiary centers increased the detection rate to 71%. (33) Furthermore, PIs were measured using an automated data selection method in healthy newborns during CCHD screening at 24 hours. (34) The median PI in asymptomatic newborns 24 hours after birth was 1.8 with a narrow interquartile range of 1.2 to 2.7. The median preductal PI was significantly higher than the median postductal PI (1.9 vs 1.8, P=.03) but this difference may not be clinically significant.

DECREASE IN INFANT CARDIAC DEATHS

A study from December 2017 (35) shows that statewide implementation of mandatory policies for newborn CCHD screening was associated with a significant decrease in infant cardiac deaths between 2007 and 2013 compared with states without these policies. In the United States, CCHD deaths dropped 16.8%, while other/unspecified cardiac deaths dropped 13.2% after screening was instituted. The authors also looked specifically at the 8 states that implemented mandatory screening policies between August 2011 and June 2013. They found a 33.4% relative decrease in CCHD deaths relative to previous years and other states, a decrease of 3.9 deaths per 100,000 births. Deaths from other/unspecified cardiac causes decreased 21.4% in states with mandatory screening relative to other states, with an absolute decline of 3.5 deaths per 100,000 births. (35) Therefore, the evidence is now sufficient to declare newborn screening for CCHD a successful public health intervention. Nearly all states now have CCHD screening requirements for all term infants who appear healthy and are asymptomatic.

WHAT TO DO WITH PRETERM INFANTS

The approach of Spo_2 screening in preterm infants is a somewhat separate issue, with individual provisos. If the preterm infant seems healthy, is asymptomatic, and does not require intensive care, screening should be conducted as described here, within 6 to approximately 24 hours, without delay or waiting for any specific postmenstrual age. On the other hand, if the preterm infant is sick and is admitted to an intensive care unit, the infant will have adequate continuous Spo_2 monitoring and careful daily evaluations during the hospital

TABLE 2. Points to Remember About CCHD Screening

- CCHD is the most common birth defect, affecting approximately 8 in 1,000 live-born children; it is estimated that about 40,000 infants are born with CCHD per year in the United States, and 1.35 million worldwide, including ductal-dependent lesions that affect between one-quarter and one-third of these children.
- CCHD represents about 40% of deaths due to congenital malformations and most deaths from cardiovascular disease occurring in the first year of age. Unfortunately, some neonatal deaths in more than 30% of infants with CCHD have been attributed to errors in diagnosis or late diagnosis.
- The prenatal diagnosis of CCHD can improve perinatal outcomes for certain lesions. (45)(46) Recent evidence shows that prenatal detection of CCHD has progressively increased from 2006 to 2012, but also that prenatal detection is highly variable.
- The prenatal diagnosis of CCHD can improve perinatal outcomes for certain lesions.
- Cyanosis is not a very reliable clinical sign to detect hypoxemia.
- The active approach of pulse oximetry with SET can achieve an improvement in the quality and safety of health care, as well as cost savings.
- Early diagnosis of CCHD in postnatal life significantly decreases morbidity and mortality rates.
- Early detection of CCHD and hypoxemic neonatal conditions not only reduces the suffering of children and families, but can also reduce associated costs and long-term neurologic compromise by not delaying admission to a specialized care unit. Early diagnosis is also associated with significant reductions in mortality, better surgical outcomes, less prolonged ventilation, and lower potential developmental problems.
- It is an obligation and responsibility of neonatal centers to improve care on a universal basis whenever possible, without waiting for laws or bureaucratic processes that often place other interests above the needs of the newborns.

CCHD=critical congenital heart defects; SET=signal extraction technology.

stay. In most infants, if not in all of them, diagnosis of CCHD is likely to be made early in the infant's course. However, if there is any doubt, a complete screening should be performed before discharge. Obviously, if complete echocardiography has been performed, there is no need for Spo_2 screening.

CONCLUSION

In summary, significant reductions in pediatric mortality, better surgical outcomes, less prolonged ventilation, and diminished potential developmental problems can occur if hospitals adopt Spo_2 screening in neonates for early and timely detection of CCHD and other hypoxemic conditions. (11)(15)(26)(27)(28)(36)(37)(38)(39)(40)(41)(42)(43)(44) Table 2 lists the most important factors to remember about Spo_2 screening. Clinicians can use the specific Spo_2 screening protocol described herein or modify the approach to specific scenarios (eg, elevated altitude). At the beginning of establishing a screening program for CCHD, each center must use a clear protocol with a quality improvement process to confirm that 100% of newborns are screened. The detection of non-CCHDs and other disorders, such as respiratory problems or early sepsis, should also be measured and reported as an additional benefit. Physicians should be aware that, even though the combination of early detection with pulse oximetry and other methods of evaluation reduces diagnostic errors, some infants might still be discharged without a proper diagnosis. Most studies indicate that the most frequently undiagnosed lesions are those that cause obstruction to the outflow of the aorta (eg, coarctation of the aortic arch), which are not necessarily associated with hypoxemia. The use of the preductal and postductal saturation difference and the PI improve detection rates, but published studies have warned that this combined technique is also not infallible. The combined approach of using Spo_2 with SET, staff education, and a focus on family support can lead to an improvement in the quality and safety of health care for newborns along with lower associated costs.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know how to interpret arterial blood gas measurements and noninvasive methods for estimating arterial oxygenation.
- Know the indications, limitations, and techniques for newborn screening for genetic disorders.

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1 Neck Swelling in a Neonate

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PRESENTATION

A 32-day-old term African American male infant presents to the emergency department with a 1-day history of congestion and fussiness. The mother notes that his 2 siblings had a cold about 2 weeks ago, but she denies fever, cough, vomiting, diarrhea, and rashes. The infant has been breastfeeding without issues and has had a normal number of voids/stools. Earlier that morning, the infant had been taken to his pediatrician's office for his fussiness and was prescribed simethicone for possible gas-related symptoms. Later that afternoon, the infant's father had noted neck swelling on the right that spread toward the left side and he was brought to the emergency department.

His initial vital signs include a rectal temperature of 100.5°F (37.7°C), heart rate of 194 beats/min, respiratory rate of 46 breaths/min, oxygen saturation of 98% on room air, and a blood pressure of 98/50 mm Hg. The patient is well appearing and in no acute distress. His lungs are clear to auscultation, a II/VI systolic murmur is heard best at the left sternal border, and abdominal examination findings are normal. He has submental/neck fullness (right greater than left) with no erythema, warmth, masses, or fluctuance noted. No lymphadenopathy is appreciable on examination.

On further history taking, the mother states that the neonate was born at 38 weeks of gestation via uncomplicated vaginal delivery. She was group B *Streptococcus* (GBS) positive and had been inadequately treated. The neonate was observed after birth without antibiotics and was discharged from the hospital when vital signs and examination results were noted to be normal. In addition, prenatal ultrasonography had shown a "hole" in the heart, but because no murmur had been heard after birth, he did not undergo follow-up echocardiography. The patient has an appointment with cardiology next week.

In the emergency department, a full evaluation for sepsis is performed including blood, urine, and cerebrospinal fluid studies given the rectal temperature of up to 100.5°F (37.7°C) on presentation. The complete blood cell count shows a white blood cell (WBC) count of 11,700/μL (11.7×10^9/L) with 61% neutrophils and 16% bands. Urinalysis shows 4 WBC per high power field, with a protein concentration of 0.03 g/dL (0.3 g/L) and glucose concentration greater than or equal to 500 mg/dL (27.7 mmol/L) with negative ketones. Cerebrospinal fluid studies show a WBC count of 3/μL and red blood cell count of 16/μL with a protein concentration of 0.04 g/dL (0.4 g/L) and glucose concentration of 99.0 mg/dL (5.5 mmol/L). The basic metabolic panel shows a glucose concentration of 162 mg/dL (9 mmol/L). Ultrasonography of the neck shows bilateral cervical adenopathy measuring 1.36×0.42 cm on the left and 1.32×0.68 cm on the right (Fig). No focal fluid collections are noted. The initial differential diagnosis includes infectious conditions such as abscesses and adenitis, congenital lesions such as thyroglossal duct cyst, and angioedema/allergy, as well as normal infant fat distribution.

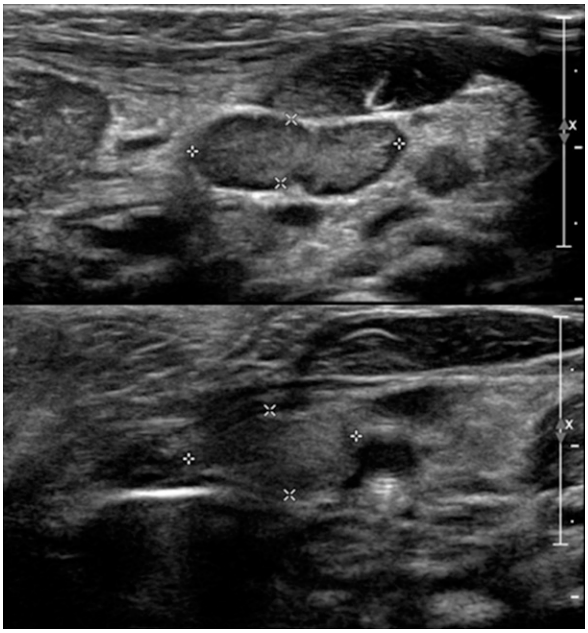

Figure. Ultrasonographic scan demonstrating prominent cervical lymph nodes.

The neonate is admitted to the pediatrics department and an ear-nose-throat specialist is consulted, who evaluates the patient and recommends coverage for infectious etiology without concern for congenital causes for neck swelling such as branchial cleft/thyroglossal duct cysts. An infectious disease specialist is consulted via telephone and recommends empirical coverage with clindamycin and ceftriaxone.

Within 12 hours of starting antibiotic therapy, the patient's neck swelling markedly improves, and the blood culture begins to grow gram-positive cocci in pairs/chains. As the swelling improves, lymphadenopathy is appreciable along the anterior cervical chain. Echocardiography shows a patent foramen ovale as opposed to atrial septal defect and bilateral pulmonary artery branch stenosis. Repeat urinalysis shows resolution of the glycosuria thought to be secondary to elevated serum glucose from stress. The fever resolves and the patient continues to eat, void, and pass stools as usual. The preliminary blood culture finding is positive for group B *Streptococcus agalactiae* sensitive to penicillin and the antibiotic treatment is narrowed to ampicillin. Repeat blood culture performed after the antibiotic course remains negative. Intravenous antibiotics are continued for 7 days and the patient makes a transition to oral amoxicillin for 3 more days for a total course of 10 days. The diagnosis of late-onset GBS bacteremia with cervical lymphadenitis is made.

DISCUSSION

In infants, GBS typically presents as early-onset disease (disease that presents before 7 days of age), late-onset disease (up to 89 days after birth), and late-late onset disease (up to 6 months of age). (1) Early-onset disease is the most common, accounting for about 60% to 70% of all GBS disease. (2) Late-onset and late-late onset disease are less common. The types of presentations for GBS are shown in the Table.

TABLE. **Presentations of Group B *Streptococcus* (1)**

Early-onset disease
• Bacteremia (most common at 80% to 85%)
• Pneumonia (10% to 15% of presentations)
• Meningitis (5% to 10% of presentations)
Late-onset disease
• Bacteremia (65% of presentations)
• Meningitis (25% to 30% of presentations)
• Other (pneumonia, cellulitis, osteoarticular infections)
Late-late onset disease
• Bacteremia

For early-onset disease, the pathogenesis involves vertical transmission from the mother to neonate. Some theorize that bacteremia results from inhalation of infected amniotic fluid and/or genital secretions into the lungs, where the GBS β-hemolysin promotes lung epithelial cell invasion and then subsequent invasion into the blood. (3) However, the pathogenesis of late-onset disease is less well understood. Intrapartum antibiotic prophylaxis has shown to help prevent early-onset disease, but has had no effect on the incidence of late-onset disease. (4)

Late-onset disease is less common than early-onset disease. The current patient presented with adenitis, which is an even less common presentation of GBS. However, this case does fit the timeline for cellulitis and adenitis of late-onset disease, because the peak incidence is generally around 5 weeks of age and the condition has a male predominance. The drug of choice for treatment of proven GBS infections is penicillin. Length of treatment depends on the site of infection, ranging from 10 days for bacteremia without a focus to 4 weeks for osteomyelitis. (1)

Lessons for the Clinician

- The diagnosis of late-onset group B *Streptococcus* (GBS) infection should be considered in infants between 1 week and 3 months of age presenting with neck swelling.
- Antibiotic coverage should be broad on initial presentation, with narrowing within 24 to 48 hours once GBS and sensitivities are confirmed.
- Index of suspicion for invasive disease in neonates always needs to be high given that these infants can initially appear well.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, prevention, and pathogenesis of perinatal/neonatal group B streptococcal infections.
- Know the clinical manifestations and diagnostic criteria of group B streptococcal infections.

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Case 1: Neck Swelling in a Neonate

Hannah Kim and Wendy Hoffner

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2 Vesicular Lesions of the Oral Mucosa

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AUTHOR DISCLOSURE Drs Weber, Delle Donne, and Delaney have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term female infant (39+4 weeks) with a birthweight of 3,055 g is born via spontaneous delivery to a gravida 4, para 3 woman. Maternal history is significant for Ashkenazi Jewish heritage and known connective tissue disease requiring plaquenil. Maternal serologies and prenatal testing are unremarkable with the exception of herpes simplex virus (HSV) 1 immunoglobulin (Ig) G being positive and IgM inconclusive. The mother was not taking antiviral therapy during pregnancy or at delivery. On admission to the labor and delivery department, the infant's mother is without prodromal symptoms or genital lesions concerning for HSV. The patient is born via spontaneous vaginal delivery through meconium-stained amniotic fluids, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. At the time of delivery, the infant has normal physical examination findings and is kept in the mother-baby unit for routine newborn care.

At about 30 hours after birth, the newborn team is called to the bedside by the nurses because of the development of vesicular lesions on the oral mucosa of the lower lip (Fig). On examination of the oral mucosa, multiple vesicular lesions are noted, which measure 1 to 2 mm in size. Because of the history of HSV-1 without antiviral suppression and the character of the lesions, a full evaluation for HSV (skin-eye-mouth disease vs disseminated disease) is initiated, and the infant is transferred to the NICU. Cerebrospinal fluid (CSF) and blood specimens are obtained for HSV polymerase chain reaction (PCR) testing. Skin and mucosal swabs for viral cultures are completed. Laboratory testing is ordered for complete blood cell count, C-reactive protein, and comprehensive metabolic panel for further screening. High-dose acyclovir is started for empirical coverage while results are pending. Dermatology and pediatric infectious disease (ID) specialists are consulted for further evaluation.

DIFFERENTIAL DIAGNOSIS

HSV presents with clear vesicular lesions that can present on the skin, eyes, or mucosa. HSV can also cause a disseminated infection. (1) Maternal infections can be passed to neonates, with mortality rates of up to 29%, even with treatment. (1) Whenever HSV is suspected, the standard of care is to empirically treat with high-dose acyclovir. Neonates must be treated until maternal testing shows negative results or empirical treatment is given for 14 to 21 days pending clarification of primary versus secondary infection. (2) HSV can be diagnosed with PCR, direct fluorescent antibody (DFA), and viral cultures. Histologic studies show reticular epidermal degeneration, acanthosis, and intraepidermal vesicle formation. Other findings include intranuclear inclusion bodies and multinucleate giant keratinocytes. (3)

Other benign entities that could present with vesicular lesions, as in this patient, are lymphangiomatous malformations and sebaceous hyperplasia. Microcystic

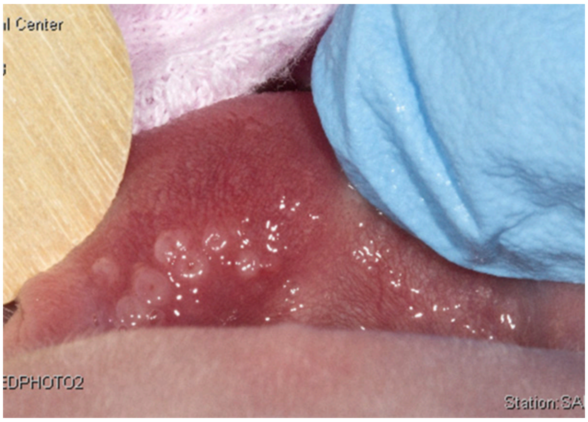

Figure. Vesicular lesions of oral mucosa.

lymphangiomatous malformations are benign tumors of the lymphatic system. Lesions are deep-seated vesicles described as "frog-spawn." Vesicles can be clear to purple in color. These lesions grow slowly and may bleed. For large malformations, surgery may be required. Histologic studies show dilated lymphatic vessels with dilated blood vessels in the upper dermis. (3)

Sebaceous hyperplasia presents with yellow-white micropapules with central umbilication. Sebaceous hyperplasia is a benign growth that can be present at birth and usually resolves within the first few weeks after birth. (4) Sebaceous hyperplasia is thought to be caused by maternal androgen levels. Histologic studies show proliferation of sebaceous lobules in the dermis.

DIAGNOSIS

The patient was ultimately diagnosed as having sebaceous hyperplasia. Sebaceous hyperplasia is a relatively common finding in newborn infants. Most cases of sebaceous hyperplasia resolve spontaneously as maternal androgen levels decrease in the infant. (4) Although a benign dermatologic finding resolves, one cannot rule out other causes when initial lesions appear as vesicles. When diagnosed with sebaceous hyperplasia, infants do not routinely need dermatology follow-up.

PROGRESSION

The infant received high-dose acyclovir for 4 days while undergoing an evaluation for HSV. Dermatology evaluated the infant and further described lesions as white-yellow papules without scarring. A lesion was unroofed with mucoid fluid expressed and a sample for HSV DFA was obtained. Based on clinical findings, dermatology diagnosed the infant as having sebaceous hyperplasia; treatment with acyclovir was recommended until the PCR test result was obtained. Pediatric ID evaluated the patient after the initial dermatology consultation and was unable to evaluate initial vesicles before unroofing. Based on the consultation with ID, the lesions were more consistent with sebaceous lesions than with HSV. In addition, ID noted that maternal HSV IgG would be largely protective against congenital infection. Perinatal HSV is very rare in the first 1 to 2 days after birth and the lack of maternal genital lesions at birth, absence of cutaneous lesions in the infant, as well as the lack of any clinical signs of infection made a diagnosis of HSV less likely. A skin biopsy specimen was taken and sent for pathologic examination but was of insufficient size and thus inconclusive. CSF and blood PCR testing and DFA for HSV were negative and the infant remained well appearing without developing further lesions. The infant was discharged from the hospital on day 4 after birth.

Three weeks after birth, the mother reported that the infant's oral lesions had fully resolved without recurrence.

Lessons for the Clinician

- A thorough physical examination, including of the oral mucosa, is important in all neonates.
- Vesicular lesions are concerning for herpes simplex virus (HSV) infection of the skin-eye-mouth, but can be consistent with benign dermatologic diagnoses.
- When concerned about HSV, it is important to aggressively treat because of the high mortality rates.

Note: The views expressed herein are those of the authors and do not reflect the official policy or position of Brooke Army Medical Center, the US Army Medical Department, the US Army Office of the Surgeon General, the Department of the Army or the Department of Defense or the US Government.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the etiology and differential diagnosis of bullous skin lesions.

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Case 2: Vesicular Lesions of the Oral Mucosa

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3 Abdominal Rash After Removal of Umbilical Vessel Catheter Anchor in a Preterm Infant

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AUTHOR DISCLOSURE Drs Ou, Kurtom, and Mitchell have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 635-g female infant is born at 25 weeks of gestation to a 36-year-old gravida 1, para 0 woman. The infant is twin B of a monochorionic-diamniotic twin gestation. The pregnancy is complicated by intrauterine growth restriction in twin A and polyhydramnios in twin B. The woman is a carrier for Gaucher disease and α_1-antitrypsin deficiency and the family history is noncontributory. Prenatal screening for syphilis, human immunodeficiency virus, hepatitis B, hepatitis C, and *Toxoplasma* are negative and rubella immune. Group B *Streptococcus* status is unknown. Maternal history is negative for herpes simplex virus (HSV) and she denies having any lesions before or during pregnancy. The infants are born via emergency delivery because of the reversal of flow on umbilical arterial Doppler ultrasonography performed for twin A; rupture of membranes occurs at delivery. The infant's Apgar scores are 6 at 1 minute and 7 at 5 minutes. Vital signs are within normal limits, and physical examination findings at birth are unremarkable. On admission to the NICU, she develops severe respiratory distress necessitating intubation, surfactant administration, and synchronized intermittent mandatory ventilation. An umbilical venous catheter is placed and reinforced with an umbilical vessel catheter anchor. A blood specimen is obtained for culture and empirical antibiotic given for respiratory distress. On postnatal day 2, she is switched to high-frequency oscillatory ventilation because she is hypercapnic. Echocardiography reveals a large patent ductus arteriosus with bidirectional shunting, which subsequently closes on postnatal day 5 after 5 doses of ibuprofen. On postnatal day 7, the umbilical venous catheter and anchor are removed and the skin to the right of the umbilicus abraded. On postnatal day 14, the medical team notices new pustular and vesicular lesions (Fig) on her abdomen over the same area. Further laboratory investigations confirm the diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the current patient's vesiculobullous rash includes bullous impetigo, group A and group B streptococcal infection, fungal infection, congenital syphilis, congenital varicella syndrome, and HSV infection. Impetigo appears pustular or as erythematous papules that later develop honey-colored crusting and is often seen in areas of previous trauma, as could have occurred after removal of the umbilical vessel catheter anchor. Although rare, group B

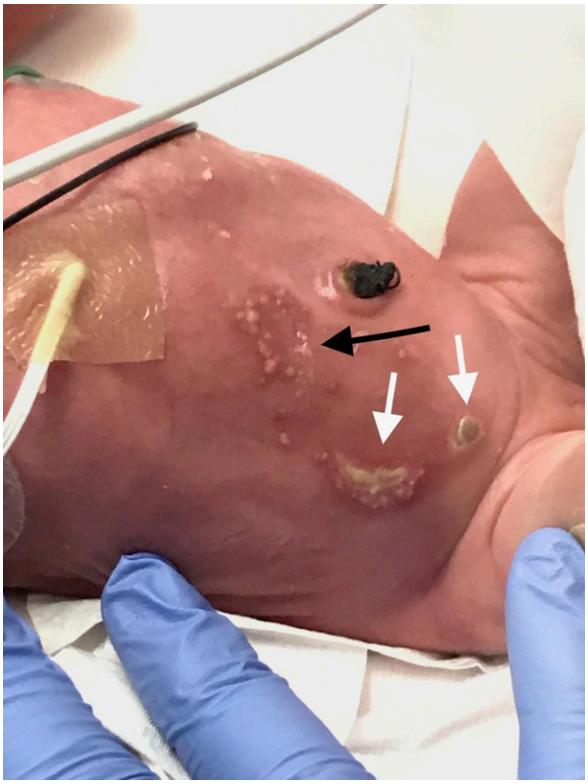

Figure. Pustular (white arrows) and vesicular (black arrow) lesions on the right side of the abdomen.

streptococcal infections can cause a bullous rash as well. *Candida* infections are the most common type of fungal infection and can cause erythematous lesions with discrete or confluent erythematous papules and plaques. The skin lesions in congenital syphilis can be seen at birth or present within 4 to 8 weeks after birth and typically involve the hands and soles. (1) One percent to 2% of infants born to mothers with varicella infection acquired between 8 and 20 weeks of pregnancy will have congenital varicella syndrome, which is characterized by vesicular lesions and cicatricial scarring, chorioretinitis, microphthalmos, nystagmus, limb hypoplasia, and central nervous system (CNS) damage when it does not cause death. (2)

Congenital cytomegalovirus presents in 1% of newborns and is the most common congenital viral infection in the United States. (1) Although most infants are asymptomatic, 10% of patients develop symptoms such as jaundice, hepatosplenomegaly, microcephaly, seizures, and sensorineural hearing loss. Skin manifestations are characteristically petechial and purpuric in nature, unlike the vesicles seen in our patient, and typically appear with other symptoms, rather than in isolation. (3)(4)

In our patient, the vesiculobullous lesions appear most consistent with HSV lesions, potentially precipitated by the skin breakdown caused by removal of the umbilical vessel catheter anchor. Prenatal screening for *t*oxoplasmosis, *o*ther agents, *r*ubella (also known as German measles), *c*ytomegalovirus, and *h*erpes simplex (TORCH) syndrome reveals patients to be HSV-1 immunoglobulin (Ig)G positive, HSV-2 IgG negative, HSV-1/2 IgM positive. These immunoglobulin concentrations are not conclusive for the diagnosis or timing of maternal disease; HSV polymerase chain reaction (PCR) had not been performed on the mother prenatally. In addition to viral cultures from the patient's skin lesions, surface viral cultures from the eyes, nasopharynx, and rectum are sent and are negative. A blood PCR for HSV, cerebrospinal fluid (CSF) specimen for cells, chemistries, Gram stain, and aerobic culture are also obtained and found to be negative. The Tzanck smear from the skin lesions is positive for multinucleated giant cells, which can be seen in herpes or varicella infections. Acyclovir and vancomycin treatment are started; vancomycin is discontinued when cultures remain negative for 2 days. She is treated with parenteral acyclovir 60 mg/kg per day for 21 days and oral suppressive acyclovir for 6 months, which has been shown to improve neurodevelopmental outcomes in CNS disease and prevent the reactivation of cutaneous manifestations. (5) CSF PCR for HSV is performed and found to be negative before the completion of parenteral therapy.

DISCUSSION

The incidence of neonatal herpes ranges between 1 in 3,000 and 1 in 20,000 live births. Neonatal herpes can manifest in 3 forms, with potential overlap between the categories: 1) disseminated disease, most commonly involving the liver and lungs, but also CNS—occurring in 20% of HSV cases; 2) localized CNS disease—30%; or 3) disease localized to the skin, eyes, and/or mouth (SEM disease)—45%. The best morbidity and mortality outcomes occur with SEM disease. Most infants with CNS disease survive but will have substantial neurologic consequences. Thirty percent of infants with disseminated disease and 6% of infants with CNS disease die even when treated appropriately with acyclovir. (1)

Understanding the potential risks and modes of HSV transmission may guide clinical judgment and increase the clinician's awareness of possible neonatal infection. Transmission most commonly occurs through contact with the maternal genital tract; however, it can also occur via ascending infection through ruptured or even intact amniotic membranes. Rarely, intrauterine infections can cause congenital malformations, and postnatal transmission from a parent or caregiver, likely from the hands or mouth, can occur. (6) Using cesarean delivery as the method of delivery decreases the risk of transmission through genital contact, but given the other potential modes of transmission, the clinician should not feel completely reassured that no transmission has occurred simply because of the cesarean delivery. One study found that the incidence of HSV infection in infants with mothers with HSV is 7.7% when delivered vaginally, and that although decreased, 1.2% of infants delivered via cesarean still develop an HSV infection. The risk of transmission is significantly higher in mothers who acquire HSV later in pregnancy compared with those who acquire HSV earlier in the pregnancy or before pregnancy. Because of the high efficiency of transmission of newly acquired HSV, 50% to 80% of neonatal HSV cases result from genital HSV acquired relatively soon after delivery, despite the fact that more infants are born to women with long-established HSV-2. (7) Although there is a correlation between the length of time from when an infection is acquired and the avidity of the infection and its efficiency of transmission, there are limitations to the practical application of this knowledge. First, it is difficult to determine the timing of maternal acquisition based on history or physical examination findings. As many as 75% of infants who acquire HSV infection are born to women with no history or physical examination findings suggestive of genital HSV infection. (1) These women are therefore unaware of their infection. Second, the physical examination findings of symptomatic women with HSV infections, such as vaginal discharge, genital pain, and shallow ulcers, are nonspecific and therefore difficult to diagnose. (8) Inquiries about the sexual partner's history of HSV can aid decision-making when the mother does not have any history or physical examination findings.

Maternal seropositivity is associated with decreased risk of transmission, because seronegativity corresponds to infants who lack transplacental antibodies and indicates primary HSV-1/2 infection and thereby a higher risk of transmission. In addition, the rate of transmission of HSV-1 appears to be higher than that of HSV-2. Previously, HSV-2 was the primary cause of genital infections, but currently, HSV-1 accounts for more than 50% of genital infections. Conversely, women with an HSV-2 infection before pregnancy are at a low risk of transmitting HSV-2; previous HSV-2 infection also has a protective effect against the transmission of HSV-1. Other risk factors for neonatal HSV include HSV isolation from the cervix, invasive monitoring (eg, scalp electrodes) with the potential to cause loss of skin integrity, and maternal age less than 21 years. (6)

Lessons for the Clinician

A high index of suspicion for HSV infection is important in symptomatic neonates. Unfortunately, the diagnosis can be complicated by many factors. Symptoms can present anytime in the first 6 weeks after birth; SEM and disseminated disease typically present in the first 1 to 2 weeks and localized CNS disease usually presents between the second and third weeks after birth. (1) In addition, manifestations are varied, and although they are categorized into 3 groups, the categories may have overlapping symptoms and can include respiratory distress, seizures, lethargy, shock, liver failure, or coagulopathy, with only two-thirds of those with disseminated or localized CNS disease also presenting with skin lesions. (1)

The diagnosis is further obscured in premature infants, as in the 25-week infant described here. Her nonspecific symptoms may be secondary to HSV infection, but could also be explained by the other morbidities that accompany prematurity, such as respiratory distress syndrome or patent ductus arteriosus. There are few studies that focus specifically on premature infants. One retrospective study with infants at a mean gestational age of 27 weeks found that premature infants tend to have more severe disease manifestations; they are more likely to have disseminated and CNS disease, rather than SEM disease. The immaturity of the innate immune system and lack of transplacentally acquired immunity could lead to more disseminated disease, because the maternal transfer of antibodies does not begin until 20 to 22 weeks' gestational age. The symptoms most commonly found in premature neonates are respiratory distress, hypotension/poor perfusion, and lethargy. (9)

In the present case, the mother did not have a history of HSV. Therefore, when vesicular and bullous lesions were noted on postnatal day 14, the differential diagnosis was broad but included HSV infection. With the maternal serologic findings in this case, IgG-positive, HSV-2 IgG-negative, HSV-1/2 IgM-positive HSV-1, we are not able to definitively determine whether the mother has a reactivated HSV-1 infection or a nonprimary first-episode HSV-2 infection. Because of the homology between HSV-1 and HSV-2 (50% shared base pairs), differentiating between HSV-1 and HSV-2 IgM is not possible with the test used. IgM is not recommended in screening, because the sensitivity is low (79% in one study). (10) In addition, the specificity of the serologic tests is lowered by cross-reactivity with the IgM of other viruses. In the test used by our laboratory, cross-reactivity has been reported with Epstein-Barr virus, cytomegalovirus, and *Toxoplasma* IgM. When present in high levels, rheumatoid factor and antinuclear antibody can also interfere with the test.

Despite the nuances involved in interpreting the clinical significance of the serologic tests, these results heighten our suspicion for HSV SEM disease acquired during pregnancy, at birth, or after birth. An initially reassuring aspect of our patient's history was the cesarean delivery with rupture of membranes at the time of delivery, but transmission can still occur with an ascending infection without rupture of membranes. (6) As discussed before, the clinician's index of suspicion must remain high despite the cesarean delivery and negative maternal history, because neither factor definitively rules out HSV transmission.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster.

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Case 3: Abdominal Rash After Removal of Umbilical Vessel Catheter Anchor in a Preterm Infant

Jocelyn Ou, Waleed Kurtom and Charles Mitchell

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A Pulsating Chest

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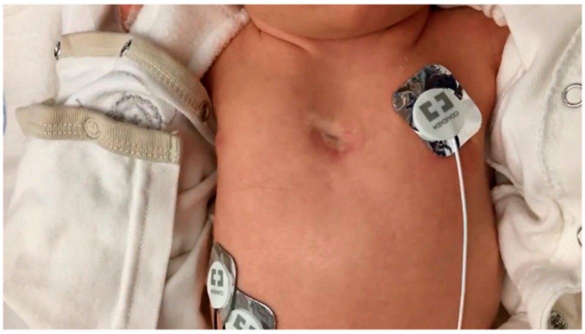

Video. Click here to view the video.

After watching the video clip (Video), further evaluation for this infant should include 1 or more of the following:

A. Echocardiography
B. Ophthalmologic examination
C. Renal ultrasonography
D. Skeletal survey
E. Upper gastrointestinal series

CRITIQUE

Case

The female infant in this video clip was born at 39 weeks' gestation to a 40-year-old gravida 4 para 2 woman with normal prenatal findings. The infant was delivered via cesarean following a fetal heart rate tracing with variable decelerations. The infant required continuous positive airway pressure for 3 minutes. Her Apgar scores were 8 and 9 at 1 and 5 minutes of age, respectively. Her birth parameters included a weight of 3,700 g (84th percentile), length 53.0 cm (98th percentile), and occipitofrontal circumference 35.5 cm (91st percentile).

Her physical examination findings were notable for a sternal defect with pulsations. Because of this finding, she was transferred to the NICU, where she initially required supplemental oxygen via high-humidity nasal cannula, but was quickly weaned to room air within a few hours. The video clip was obtained shortly after the infant was admitted to the NICU. The clip depicts a newborn with a U-shaped defect in the superior aspect of the sternum with a membranous defect over the xiphoid. The sternum collapses posteriorly during inspiration. Pulsations can be seen under the membranous defect between respiratory efforts. The skin over the sternal defect is normal. The infant did not have any anterior abdominal wall defects and there were no other midline defects.

AUTHOR DISCLOSURE Drs Mammel and Vachharajani have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

The video findings are consistent with a partial superior type sternal cleft (SC). This is a type of chest wall malformation caused by a defect in the sternal fusion process. An SC is a rare congenital chest wall malformation with a reported incidence of less than 1% of all chest wall malformations. (1) More common chest wall malformations include a pectus excavatum (caved-in) and pectus carinatum (protrusion).

Sternal development begins during the 6th week of gestation with the formation of a pair of parallel mesenchymal bars. Between the 6th and 10th weeks of gestation, cells migrate from these 2 lateral bars to fuse and form a series of sternal bars in the midline. This process occurs in a craniocaudal direction. (2) The manubrium arises from a central presternal mass and bilateral suprasternal masses. The presternal mass fuses with the cranial aspect of the sternal bars; the suprasternal masses develop into the sternoclavicular joints. An SC results from a defect at some point in the fusion process. Inferior SC is thought to result from a failure of the fusion of sternal bars, while a superior SC may result from failure of manubrium formation. (3)

The physical examination of a newborn with an SC often shows a paradoxical midline thoracic bulging. Depending on the extent of the defect, an SC can be small and be undetected, or can be complete and associated with ectopia cordis. Infants with a partial SC are typically asymptomatic at birth, though affected infants are at increased risk of injury to the mediastinal structures, and can develop respiratory symptoms if the SC is not surgically corrected.

The phenotypic spectrum of SCs is broad; an SC can be partial or complete, superior or inferior, and can be isolated or associated with other defects. One review found that an SC was associated with other defects in 73% of cases (n=63/86). (4) Initial evaluation of an infant with an SC should include a detailed physical examination to assess for hemangiomas, cleft lip or palate, skin tags, supraumbilical raphe, and an omphalocele. If hemangiomas are found, the infant may require a laryngotracheobronchoscopy to rule out subglottic hemangiomas.

A *superior SC* can be a component of PHACES syndrome. PHACES stands for *P*osterior fossa malformations, *H*emangiomas, *A*rterial anomalies, *C*ardiac defects, *E*ye abnormalities, and *SC* and supraumbilical raphe.

An ophthalmologic evaluation and posterior fossa imaging may be indicated in a patient with an SC, particularly if hemangiomas are identified. A cardiologic evaluation is recommended in all cases. (4)

An *inferior SC* can be seen in association with pentalogy of Cantrell. The 5 anomalies found in patients with pentalogy of Cantrell consist of a(n) 1) anterior diaphragmatic defect, 2) midline supraumbilical abdominal wall defect, 3) defect in the diaphragmatic pericardium, 4) intracardiac abnormalities, and 5) defect of the lower sternum. A diagnosis of complete pentalogy of Cantrell is rare and associated with a high mortality. (5)

The infant in this video was diagnosed as having an SC immediately after birth. Physical examination did not reveal any hemangiomas. Brain magnetic resonance imaging showed a normal posterior fossa. Echocardiography revealed a small patent ductus arteriosus, which had closed on repeat imaging 2 days later. The neonate also displayed dilation on ophthalmologic examination, which was found to be normal. The infant's chromosomal microarray analysis was normal. Thus, the infant had an isolated partial superior SC. At 3 days of age, she underwent primary closure without hemodynamic or respiratory compromise. Postoperatively, she was observed in the cardiac intensive care unit for 44 hours and then transferred back to the NICU before discharge.

CORRECT RESPONSES

A and B. Based on the clinical findings of a superior partial SC, the infant's evaluation should include echocardiography to rule out structural cardiac defects, as well as an ophthalmologic examination to assess for eye abnormalities associated with PHACES syndrome. The infant did not have any hemangiomas on physical examination, which would raise the index of suspicion for PHACES; however, given the high rate of defects associated with an SC, it is reasonable to perform a complete evaluation.

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Does Antenatal Steroid Administration Impact Electronic Fetal Monitoring?

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal values for arterial umbilical cord gas values and indications of acidosis are defined in the Table.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave–like undulating pattern, with waves having regular frequency and amplitude

AUTHOR DISCLOSURE Drs Kilowski and Robinson have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. Arterial Umbilical Cord Gas Values

	pH	Pco$_2$ (mm Hg)	Po$_2$ (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤–10 (–2.0 to –9.0)
Respiratory acidosis	<7.20	>60	Variable	≤–10
Metabolic acidosis	<7.20	<60	Variable	≥–10
Mixed acidosis	<7.20	>60	Variable	≥–10

*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695.

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable
Minimal: Amplitude range is greater than undetectable to 5 beats/min
Moderate: Amplitude range is 6–25 beats/min
Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
    - Normal: ≤5 contractions in 10 minutes
    - Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
    - Baseline rate: 110 to 160 beats/min
    - Baseline FHR variability: Moderate
    - Late or variable decelerations: Absent

  - Early decelerations: Present or absent
  - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - ■ Recurrent late decelerations
    - ■ Recurrent variable decelerations
    - ■ Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol*. 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

A 22-year-old gravida 2, para 0-0-1-0 woman presented to the labor and delivery department at 33 1/7 weeks' gestation based on her last menstrual period, which was consistent with findings on 20-week ultrasonography. She had contacted emergency services after she felt frequent contractions that had become more painful and intense. Before these symptoms, her pregnancy had been notable only for an isolated echogenic intracardiac focus that had not required any additional follow-up because of an otherwise normal fetal survey and low-risk quadruple screen. Her 1-hour glucose tolerance test result was within normal limits. Her prenatal screening results were all negative and her blood type was O positive. Her medical or surgical history was not significant, and she denied the use of tobacco, alcohol, or illicit drugs. Her only medications were prenatal vitamins. Her family history was noncontributory.

Upon evaluation, she denied vaginal bleeding or leakage of fluid, and endorsed feeling fetal movement. Vital signs were all within normal limits. EFM demonstrated a category I FHR tracing, with a baseline heart rate of 135 beats/min, moderate variability, accelerations present, and no decelerations. Tocometry noted contractions every 2 to 3 minutes (Fig 1).

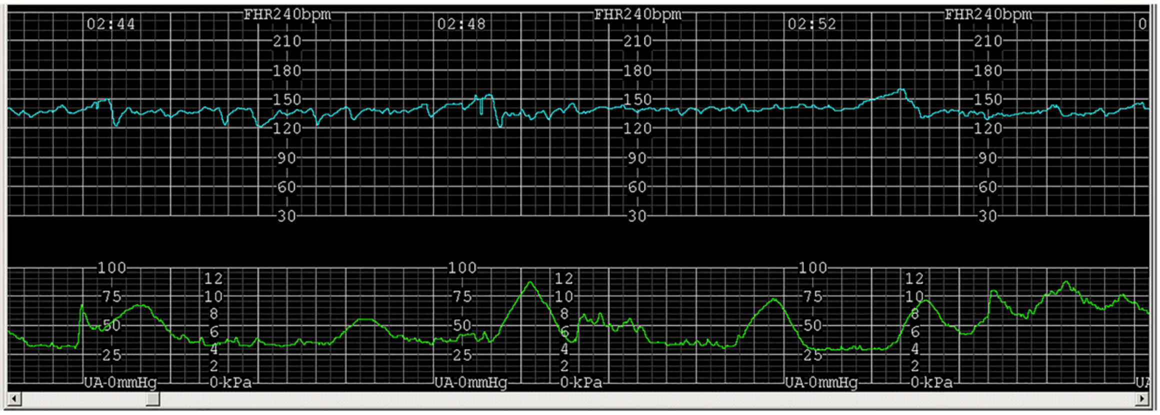

Figure 1. Electronic fetal monitoring strip 1 (category I tracing with accelerations; suspected preterm labor).

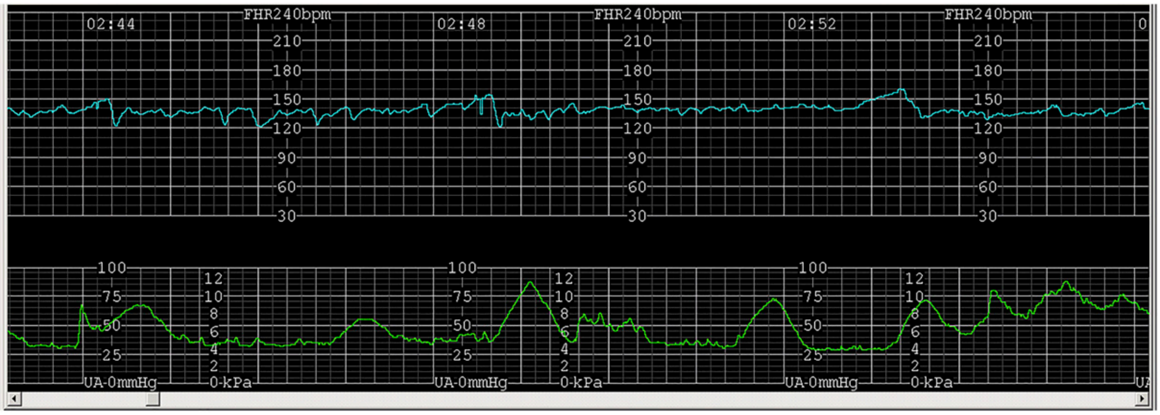

Figure 1. Electronic fetal monitoring strip 1 (category I tracing with accelerations; suspected preterm labor).

Findings on electronic fetal monitoring strip 1 were as follows:

- Variability: Moderate
- Baseline rate: 135 beats/min
- Episodic versus periodic pattern: 2 or more accelerations present; no decelerations present
- Uterine contractions: Every 2 to 3 minutes
- Interpretation: Category I tracing
- Differential diagnosis: Category I tracing with evidence of preterm contractions
- Action: Betamethasone for fetal lung maturity; tocolysis if cervical change were to commence

An initial cervical examination showed that she was 1 cm dilated, 25% effaced, and in floating station, which was unchanged after 1.5 hours. She was given an intravenous fluid bolus, and a urine specimen was collected, which was later found to be normal. Because of her nulliparous status, uterine contractions, and dilated cervix, betamethasone was administered for fetal benefit. The patient was informed that tocolysis would be administered if cervical dilation advanced or effacement occurred. She was admitted for observation to the antepartum service. Subsequently, cervical examination showed the patient's condition to be stable, and her contractions decreased in both frequency and intensity. A sterile vaginal examination was repeated the following morning with no cervical changes noted and her contractions completely resolved. She was given a second dose of betamethasone 24 hours after receipt of the initial dose. After serial cervical examinations revealed no cervical change, she was discharged from the hospital with preterm labor precautions, and outpatient follow-up was arranged for 1 week later.

One day after discharge, the patient presented to the labor and delivery department at 33 3/7 weeks' gestation with decreased fetal movement since the previous night. She was given intravenous hydration and a repeat urinalysis result was normal. A nonstress test (NST) was noted to be nonreactive but without decelerations (Fig 2).

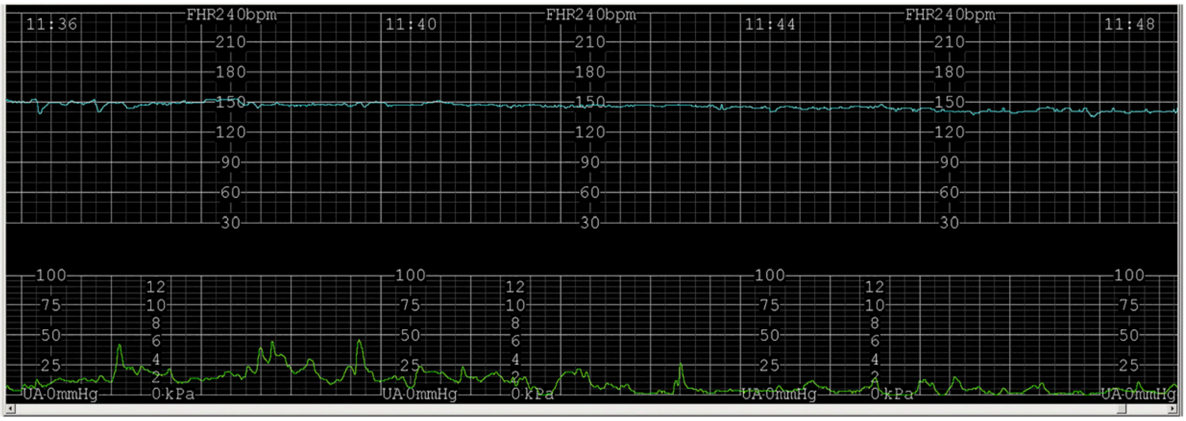

Figure 2. Electronic fetal monitoring strip 2 (time 11:38–11:46; nonreactive nonstress test with minimal variability).

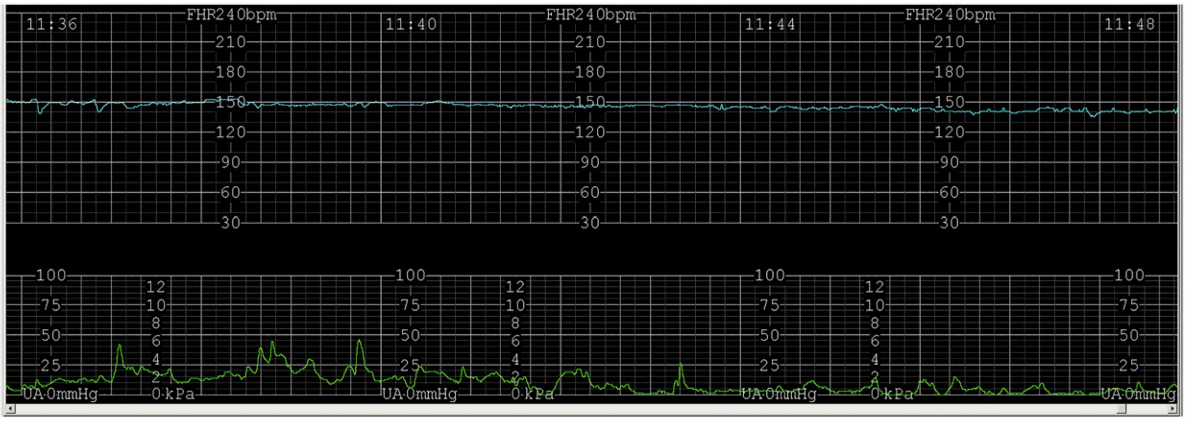

Figure 2. Electronic fetal monitoring strip 2 (time 11:38–11:46; nonreactive nonstress test with minimal variability).

Findings on EFM strip 2 were as follows:

- Variability: Minimal
- Baseline rate: 145 beats/min
- Episodic versus periodic pattern: Neither accelerations nor decelerations are present
- Uterine contractions: Irritable, no contractions
- Interpretation: Nonreactive NST
- Differential diagnosis: Fetal acidemia, pharmacologic effect, neurologic compromise, immature neurologic development
- Action: Biophysical profile (BPP) and prolonged fetal monitoring

A BPP was obtained and noted to be 6/8 (–2 for movement). Fetal ultrasonography showed an amniotic fluid index (AFI) of 22 cm and an estimated fetal weight of 2,468 g (50%). Culture specimens were obtained including group B *Streptoccocus*, gonorrhea, chlamydia, and wet mount, all of which were found to be negative. Her cervix was found to be unchanged at 1 cm dilation, long, and high. She was observed in triage where she received prolonged fetal monitoring (Fig 3).

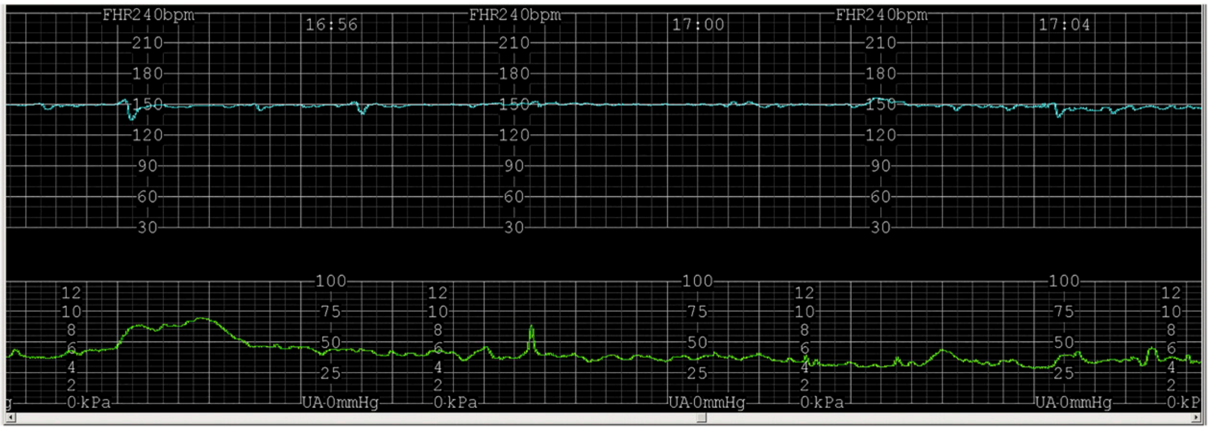

Figure 3. Electronic fetal monitoring strip 3 (time 16:55–17:03; nonreactive nonstress test with minimal variability).

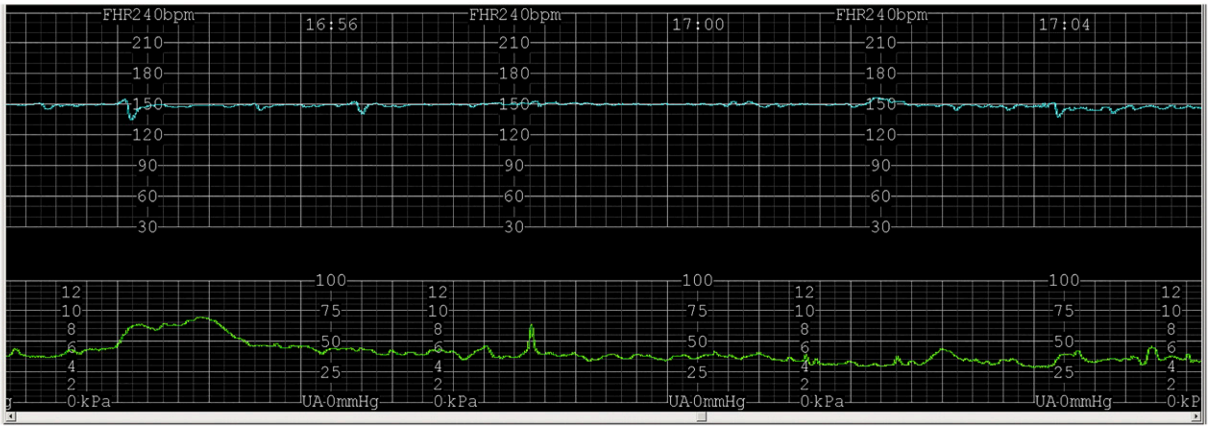

Figure 3. Electronic fetal monitoring strip 3 (time 16:55–17:03; nonreactive nonstress test with minimal variability).

Findings on EFM strip 3 were as follows:

- Variability: Minimal
- Baseline rate: 150 beats/min
- Episodic pattern: Neither accelerations nor decelerations are present
- Uterine contractions: Occasional
- Interpretation: Nonreactive NST
- Differential diagnosis: Fetal acidemia, pharmacologic effect, neurologic compromise, immature neurologic development
- Action: Plan for repeat BPP in 12 hours

Based on this fetal monitoring result, the obstetrical team planned to continue hospital observation and a repeat BPP was obtained the next morning. Overnight, the patient described intermittent cramping and was again placed on the fetal monitor. The obstetrical team performed a sterile vaginal examination and noted that her cervix was unchanged. During the night, a repeat NST was found to be reactive with a baseline heart rate of 150 beats/min, moderate variability, 15×15 accelerations, no decelerations, and an irritable pattern on tocometry (Fig 4).

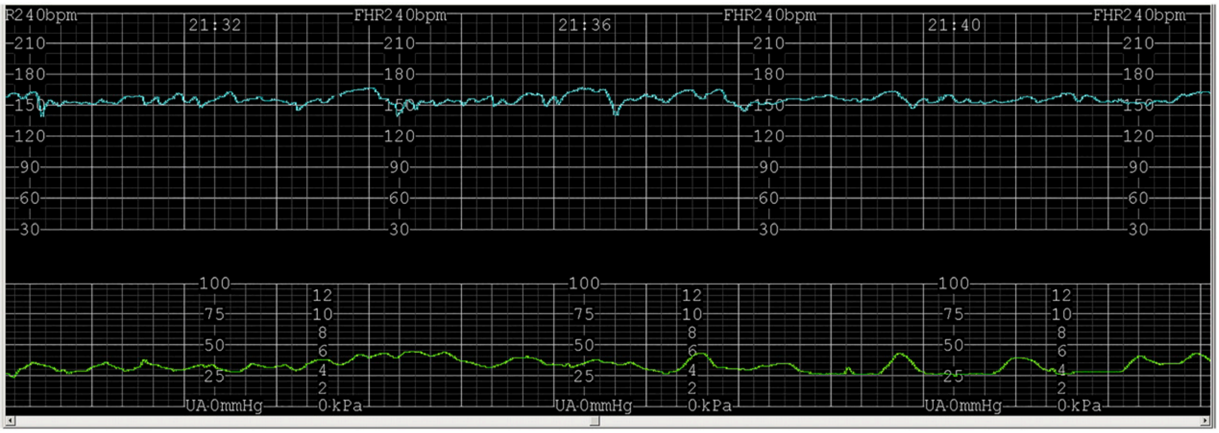

Figure 4. Electronic fetal monitoring strip 4 (time 21:32–21:40; reactive nonstress test).

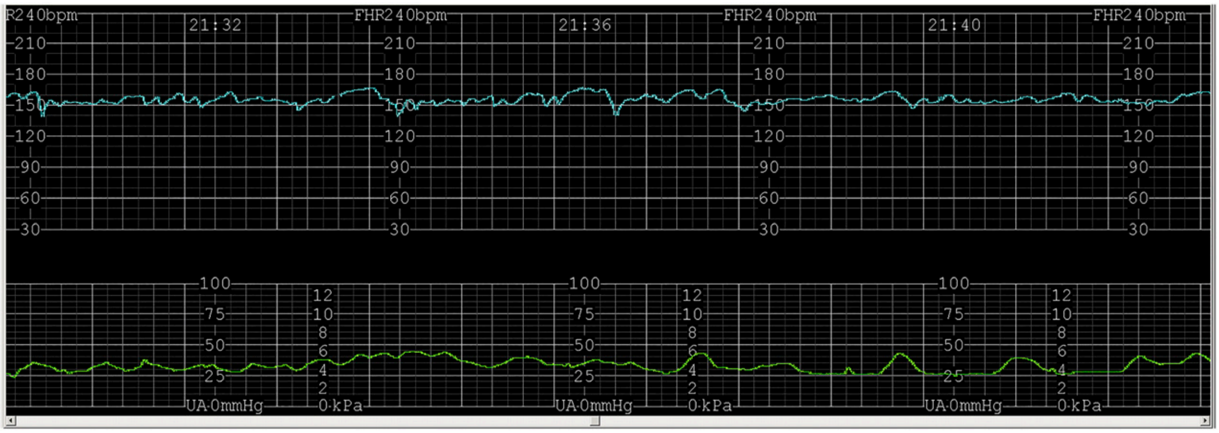

Figure 4. Electronic fetal monitoring strip 4 (time 21:32–21:40; reactive nonstress test).

Findings on EFM strip 4 were as follows:

- Variability: Moderate
- Baseline rate: 150 beats/min
- Episodic pattern: 2 or more accelerations; no decelerations present
- Uterine contractions: Absent
- Interpretation: Reactive NST
- Differential diagnosis: Reactive and reassuring fetal status
- Action: Stable for discharge with close outpatient monitoring

Because the NST was reactive, the obstetrical team was reassured about the fetal status. The following day, the patient reported active fetal movements. A repeat BPP was performed and found to be 8/8, with another NST noted to be reactive. Thus, she was discharged from the hospital with close outpatient monitoring. Her prenatal care was uneventful for the next month.

OUTCOME

At 37 3/7 weeks' gestation, the patient presented to the obstetrical office with lower extremity edema and cramping. Her abdomen was visibly distended. She was normotensive. An NST was reactive but limited ultrasonography showed an AFI of 30. Follow-up level II ultrasonography was limited because of fetal movement and degree of hydramnios, but showed the following: estimated fetal weight of 4,339 g (>90%), AFI of 40.76, and a posterior placenta. Fetal echocardiography performed at 37 6/7 weeks' gestation demonstrated a right ventricle–to–left ventricle ratio that was disproportionate, with a smaller left ventricle, concern for a hypoplastic ascending aorta and arch, an enlarged right atrium, a dilated main pulmonary artery with possible component of pulmonary stenosis, and right axis deviation. The obstetrical team was concerned that the patient may experience amniorrhexis (ie, rupture of membranes) and labor in the setting of severe polyhydramnios and potentially deliver at an institution where adequate postnatal cardiac care may not be available. Therefore labor was induced with a balloon catheter and oxytocin at 37 6/7 weeks' gestation. The patient progressed through labor before experiencing arrest of dilation at 7 cm. The FHR tracing was category I throughout her entire labor course. The decision was made to move forward with a primary cesarean delivery due to arrest of dilation.

After a cesarean delivery, the female infant emerged vigorous, was shown to her parents, and was transported to the NICU in stable condition. Her Apgar scores were 8 and 8 at 1 and 5 minutes, respectively. The umbilical arterial gas had a pH of 7.27 with a base excess of –1.2, and the umbilical venous gas showed a pH of 7.35 with a base excess of –0.9. The placenta was then delivered spontaneously with uterine massage and was found to be intact. Uterine atony was noted, which was unresponsive to medical management with oxytocin, carboprost, methylergonovine, and misoprostol. A B-Lynch suture was applied, resulting in adequate tone and hemostasis. The mother was given a transfusion of 2 units of packed red blood cells for an estimated blood loss of 2,650 mL. The nadir of her postpartum hemoglobin was 7.2 g/dL (72 g/L) on postoperative day 3 and she was discharged from the hospital with oral iron supplementation the following day.

The infant did not have any respiratory distress or cyanosis and had normal perfusion and blood pressures. The rest of her physical examination findings were notable for clear breath sounds; normal S1, S2 without murmur; soft abdomen, that was nondistended; and congenital dermal melanocytosis over her lower back and left upper thigh. An echocardiogram was obtained the following day, which was overall nonconcerning with a possible hypoplastic aortic arch. Repeat echocardiography performed a few days later had findings that were within normal limits, including a normally patent arch, widely patent proximal descending aorta, the absence of a patent ductus arteriosus, moderate flattening of the interventricular septum consistent with half-systemic right ventricular pressure, physiologic peripheral pulmonary artery stenosis, and normal biventricular wall motion. The infant's neonatal course was complicated by hypoglycemia and indirect hyperbilirubinemia, both of which resolved in a few days. She was then discharged from the hospital and advised to receive routine follow-up with the pediatrician.

DISCUSSION

This case highlights the potential effects of maternal antenatal corticosteroids on fetal status, EFM, and BPP scores. Antenatal corticosteroids are routinely administered to enhance fetal lung maturation in patients at increased risk of delivering before 34 weeks' gestation. It is well-studied that steroid administration in this population is strongly associated with lower rates of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and infant mortality. (1) What is not always appreciated is that the practice of administering steroids may in some instances obscure the interpretation of some forms of fetal surveillance that are almost universally used to monitor the well-being of the fetus at high risk of preterm delivery.

A prospective randomized trial performed by Rotmensch et al (2) evaluated the effect of betamethasone and dexamethasone on FHR and BPP. Forty-six pregnant women (all singletons) between 27 and 34 weeks' gestation who were at increased risk of preterm birth—with over half of the patients admitted for preterm labor—were given either betamethasone or dexamethasone. At the time of admission, the women were monitored with a 60-minute NST, which was repeated along with a BPP, 48 and 96 hours later. The investigators found that, 48 hours after administration, both betamethasone and dexamethasone elicited a decrease in FHR accelerations ($P<.001$ and $P<.01$, respectively), short-term variation ($P<.0001$ and $P<.05$, respectively), total movement count ($P<.001$ and $P<.05$, respectively), and duration of fetal breathing ($P<.0001$ and $P<.0001$, respectively). In 68.2% and 45.5% of patients in the betamethasone and dexamethasone groups, continuous fetal breathing movements were present for less than 30 seconds 48 hours after administration of steroids, and in 71.8% and 12.5% of fetuses, zero or only 1 limb/body movement was noted on ultrasonography 48 hours after steroid exposure. All parameters returned to baseline values at 96 hours. The authors thus concluded that administration of antenatal corticosteroids often induces a profound, though transient, suppression of FHR characteristics in the preterm fetus, with betamethasone having a more pronounced effect.

A similar prospective study by Senat et al (3) examined the FHR parameters of 82 gravida women—including 13 twin pregnancies—admitted with preterm labor between the gestational ages of 25 and 33 weeks. The women were randomly allocated to receive either betamethasone or dexamethasone. The results demonstrated that women in the betamethasone group had a decrease in FHR variability at 24 to 48 hours ($P=.01$), but that within a week, all FHR patterns returned to pretreatment levels. Interestingly, FHR accelerations were increased in the betamethasone group ($P=.01$). No significant changes were found in the dexamethasone group. The authors concluded that knowledge of these steroid-induced FHR changes is important when determining a plan of management, and that dexamethasone may be less likely to result in diminished FHR variability.

Mulder et al (4) retrospectively reviewed data from 63 women with singleton pregnancies between 26 and 34 weeks' gestation, who were at high risk of preterm delivery; they studied the effect of betamethasone on FHR tracings and fetal sonographic assessment. These authors reported a change in the baseline FHR 1 to 3 days after steroid administration ($P<.05$) and a decrease in long-term variability 2 to 3 days after steroid administration ($P<.05$), irrespective of gestational age. Fetuses with a gestational age of 30 weeks at more than or equal to 5 days were shown to have fewer body movements on ultrasound assessment 1 to 2 days after maternal steroid administration ($P<.05$) and had fewer breathing movements on ultrasonography 2 to 3 days after receipt of steroids ($P<.01$). In contrast, fetuses of lower gestational ages did not exhibit these changes. All the alterations returned to baseline values by 4 days after steroid administration.

These studies demonstrate that changes in FHR patterns and fetal behavior as assessed on ultrasonography are often a physiologic response to steroid administration. The mechanism of action has been postulated to be a glucocorticoid receptor–mediated process in the fetal brain either directly or indirectly by suppressing maternal adrenal gland activity. The secondary effects affect fetal diurnal rhythms. A 2005 study (5) supported this theory by measuring maternal adrenocorticotropic hormone and cortisol levels in 16 pregnant women between 27 and 32 weeks of gestation on days 2, 3, and 4 to 6 after 2 doses of betamethasone administration. The authors found that adrenocorticotropic hormone and cortisol levels were completely suppressed on day 2, before resumption of the normal diurnal pattern on days 4 through 6. These findings coincided with the characteristic changes in fetal cardiotocography (ie, FHR and uterine contraction patterns) and sonographic assessment as described by the group previously. (4)

Being mindful of these alterations in fetal behavior is important when managing antenatal steroid administration in pregnant women who are at risk for preterm delivery and who exhibit an otherwise inexplicable loss of certain previously reassuring FHR characteristics and sonographic fetal activities. This knowledge of antenatal steroid effect on the fetus may prevent the unnecessary premature delivery of a fetus that is actually displaying a frequently observed physiologic response to a beneficial fetal therapy.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the potential non-pulmonary effects on the fetus and/or newborn infant of maternally administered steroids (including betamethasone, dexamethasone, and prednisone).

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Parent Resources from the AAP at HealthyChildren.org

- New AAP Recommendations Aim to Ensure Safe Donor Human Milk Available for High-Risk Infants Who Need It https://www.healthychildren.org/English/news/Pages/New-AAP-Recommendations-Aim-to-Ensure-Safe-Donor-Human-Milk-Available-for-High-Risk-Infants-Who.aspx
- Health Issues of Premature Babies https://www.healthychildren.org/English/ages-stages/baby/preemie/Pages/Health-Issues-of-Premature-Babies.aspx
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Strip of the Month: Does Antenatal Steroid Administration Impact Electronic Fetal Monitoring?

Karolina A. Kilowski and Barrett Robinson

NeoReviews 2018;19;e256
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A Preterm Newborn with Abnormal Development of the Lower Abdomen and Genitalia

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Baswaraj Tandur, DCH, DNB,* Varma Vidyasagar, DCH*
**Princess Durru Sehvar Children's Hospital, Hyderabad, India*

THE CASE

A preterm newborn is noted after delivery to have abnormal development of the lower abdomen and genitalia.

Prenatal and Birth Histories

- Born to a 23-year-old, gravida 1 woman; nonconsanguineous marriage
- Conception after ovulation induction
- Normal prenatal maternal laboratory screening and fetal survey
- Pregnancy complicated by vaginal bleeding noted 5 days before delivery and preterm labor at 32 weeks' gestation
- Vaginal delivery at an estimated gestational age of 32 weeks
- Apgar scores: 7 and 9 at 1 and 5 minutes, respectively; no resuscitation was required

Presentation (Newborn Day)

Immediately after birth, the neonatology team that was present at delivery examined the infant and noted a lower abdominal mass and ambiguous genitalia (Fig 1). The infant was transferred to the NICU for further evaluation. On admission, the newborn was noted to have central cyanosis and given nasal prong continuous positive airway pressure (CPAP).

PROGRESSION

Vital Signs

- Heart rate: 140 beats/min
- Respiratory rate: 60 breaths/min
- Temperature: 96.8°F (36.0°C)
- Oxygen saturation: 90% on respiratory support of CPAP with positive end-expiratory pressure of 5 cm H_2O

Physical Examination

- Birthweight: 1,560 g (10th percentile)
- Birth head circumference: 28 cm (10th percentile)
- Birth length: 40 cm (10th percentile)
- Head: Normal, open and flat fontanelles; no facial dysmorphism; intact palate
- Lungs: Normal chest shape, mild respiratory distress with moderate intercostal retractions

AUTHOR DISCLOSURE Drs Deshabhotla, Prajapati, Tandur, and Vidyasagar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

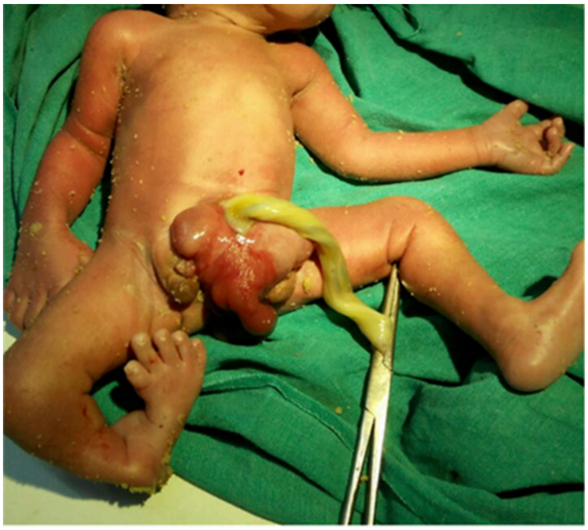

Figure 1. Exstrophy and epispadiasis.

- Cardiovascular: Normal precordial shape and heart sounds, no murmur, appropriate peripheral pulses
- Back: Soft, cystic, skin-covered swelling over right para lumbosacral region (Fig 2)
- Abdomen and genitourinary: Bilateral bladder swellings; ambiguous genitalia with bilateral bifid scrotal swellings and absent testes; incontinence of urine and stool from ectopic opening below perineum (Fig 3)
- Anus: Imperforate anus; an elephant trunk appearance of the perineum
- Extremities: Left-sided talipes equinovarus (suspected agenesis of talus)
- Hips: Left-sided hip dislocation

Laboratory Studies

- White blood cell count: 10,000/μL (10×10^9/L)
- Differential count: Neutrophils 60%, lymphocytes 35%, eosinophils 3%, basophils 2%
- Serum electrolytes: Sodium 145 mEq/dL (145 mmol/L), potassium 3.0 mEq/dL (3.0 mmol/L), chloride 110 mEq/dL (110 mmol/L)

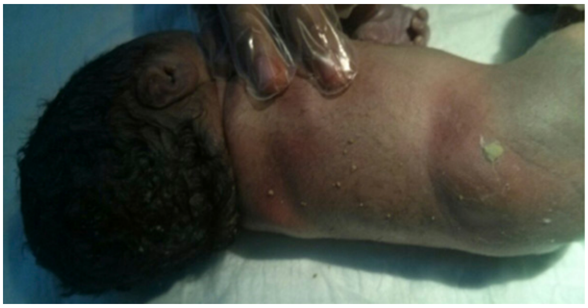

Figure 2. Syringomyelia.

- Blood urea nitrogen 32 mg/dL (11.4 mmol/L), serum creatinine 0.9 mg/dL (80 μmol/L)
- Mild metabolic acidosis
- Karyotype and genetic studies: This testing was advised but family declined due to financial constraints

Imaging Studies

- Chest radiography: Reticulogranular pattern consistent with surfactant deficiency
- Abdominal radiography: Lumbar hemivertebrae and widely spaced pubic bones
- Abdominal ultrasonography: Absent bladder, hydroureter, hydromelia in the lumbosacral region; absence of uterus, ovary, or testes; both kidneys were visualized and were normal in size and echotexture
- Echocardiography: Moderate-sized patent ductus arteriosus, no other structural abnormality
- Cranial ultrasonography: Normal

Differential Diagnosis

- Bladder exstrophy
- Omphalocele-exstrophy-imperforate anus-spinal defect (OEIS) complex

ACTUAL DIAGNOSIS

The infant was diagnosed as having OEIS complex. The infant's specific findings were identified.

MANAGEMENT

The infant received intravenous total parenteral nutrition and continued to receive CPAP until the second day after birth. The parents were counseled about the syndromic nature of the infant's condition and the concerning long-term prognosis. Because of the poor prognosis, as well as for cultural reasons, the family opted for palliative and supportive care and declined surgical interventions. The infant was transferred to a health facility closer to the family's residence and continued to receive total parenteral nutrition. The infant died at 45 days of age after developing sepsis and pneumonia.

WHAT THE EXPERTS SAY

OEIS complex is rare, with a reported incidence of 1 in 200,000 to 400,000 births. (1) OEIS complex consists of phallic separation with an epispadias, pubic diastasis, exstrophy of the bladder (exposed bladder mucosa), and cloacal exstrophy (ventral body wall defect). (2)(3)(4)

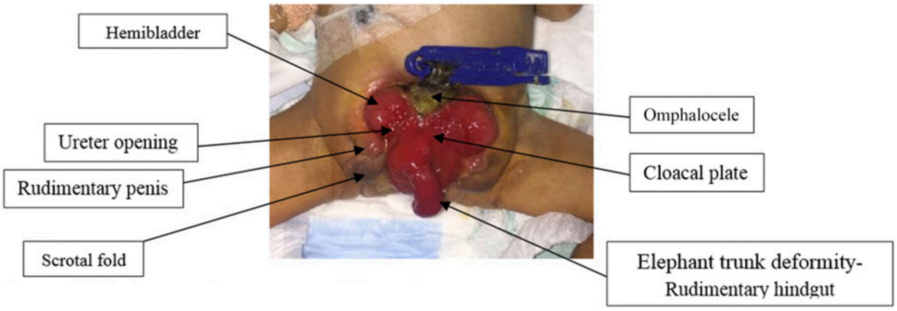

Figure 3. Elephant trunk appearance of the perineum.

OEIS is the result of an isolated defect that occurs during the early blastogenesis stage (4–6 weeks' gestation) with abnormal development of mesoderm. This contributes later in gestation to infraumbilical mesenchyme, responsible for the formation of a cloacal septum, and caudal vertebrae. Because of the abnormal infraumbilical mesenchyme development, cloacal septation does not take place. Thus, the ureters, ileum, and rudimentary hindgut open into this common cloaca. An associated maldevelopment of the lumbosacral vertebrae in the form of a dilated central canal and herniation (ie, hydromyelia) is a common finding. Abnormal formation of the urorectal septum results in the failure of the urogenital sinus to separate from the rectum. (5)

Even though the etiology of OEIS is unknown and the occurrence is sporadic, several associations have been noted, including teratogenic exposure to antiepileptic drugs, mutations in Homeobox genes (such as *HLXB9*), and chromosomal aneuploidies (eg, 47,XXX and T18). (3)(6)(7)

Associated anomalies include the following: hypoplastic chest, diaphragmatic hernia, meningocele, tethering of the cord, scoliosis, pelvic kidneys, renal agenesis, multicystic kidney, ureteral duplication, a single umbilical artery, and anomalies of the lower limbs including congenital hip dislocation, talipes equinovarus, and limb agenesis. Boys may have cryptorchidism or a bifid penis with widely separated pubic bones and affected girls have müllerian duct orifices below the bladder mucosa with completely bifid uterine horns, a bifid clitoris, and a short, duplicated, or atretic vagina. (8)

The antenatal diagnosis of OEIS is possible by identifying a midline infraumbilical abdominal wall defect with an irregular cystic mass, absence of the bladder between the 2 umbilical arteries, a lumbosacral neural or vertebral defect, abnormalities of the inferior limbs, and/or a wide pubic arch with symphysis pubis diastasis. (9)(10) Maternal serum α-fetoprotein levels may be elevated. Most cases of OEIS complex are confirmed after birth or at autopsy after the pregnancy is terminated.

Early prenatal diagnosis of OEIS complex allows clinicians to offer families the option to terminate the pregnancy. If a family decides to continue the pregnancy, early diagnosis can allow the family to meet with specialists to plan the appropriate perinatal management. Delivery by cesarean is typically recommended to avoid shoulder dystocia and trauma. During surgical repair, the omphalocele is closed, the gastrointestinal tract is separated from the hemibladders, and the hemibladders are formed into 1 viscus. If feasible, the colon can be pulled through, either at the time of this initial surgery or at a later date. The bladder must be reconstructed using the infant's stomach and a continence mechanism is constructed by narrowing the outlet and inserting a reversed small bowel nipple. Stool continence is achievable in most patients with the use of enema washouts. In most cases, experts recommend that genetic males should be raised as females as there is often inadequate tissue to create a phallus. (11) The prognosis for infants with OEIS complex is poor. (12)

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the pathogenesis and associated of omphalocele.

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ANSWER KEY FOR APRIL 2018 NEOREVIEWS

Healthcare and Societal Costs of Bronchopulmonary Dysplasia: 1. B; 2. A; 3. C; 4. B; 5. B.

Control of Breathing and Apnea of Prematurity: 1. D; 2. D; 3. D; 4. C; 5. B.

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Answer Key appears on page e311.

Corneal Opacities in the Neonate

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Education Gaps

1. Congenital corneal opacities often can be an early sign of an underlying systemic condition.
2. The visual prognosis for a newborn with a congenital corneal opacity can be significantly affected by delays in diagnosis and treatment.

Abstract

A congenital corneal opacity is a rare occurrence but can cause significant visual compromise to the affected infant. Corneal opacities can arise from infectious, metabolic, genetic, developmental, and idiopathic causes. Early diagnosis is imperative so that an appropriate treatment plan can be initiated as soon as possible to obtain the best visual potential. An early diagnosis can facilitate the recognition of an underlying systemic disorder that may also be affecting the infant. Management strategies include amblyopia treatments, refractive error correction, and surgery. Despite aggressive treatment, visual potential may still be limited in many cases.

Objectives After completing this article, readers should be able to:

1. Derive a thorough differential diagnosis for a patient with a congenital corneal opacity.
2. Recognize the signs of common causes of congenital corneal opacities.
3. Recognize the challenges associated with the treatment and management of infants born with corneal opacities.
4. Describe common components of treatment for congenital corneal opacities.

AUTHOR DISCLOSURE Dr Khitri has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CHED	congenital hereditary endothelial dystrophy
HSV	herpes simplex virus
MPS	mucopolysaccharidosis

INTRODUCTION

Congenital corneal opacification is a rare condition, occurring in 6 in 100,000 newborns globally. However infrequent, corneal opacities can have devastating consequences for a child's long-term visual potential, especially if not recognized and treated promptly. Congenital clouded cornea has various etiologic factors:

genetic, metabolic, developmental, and idiopathic. A quick and accurate diagnosis by the treating neonatal team can aid a child's visual prognosis and may also help diagnose a systemic condition or syndrome that may be affecting the infant.

CLINICAL APPROACH

When trying to decipher the cause of a congenital corneal opacification, clinicians should obtain a thorough and accurate history from the infant's parents and obstetrical staff. Many infectious processes, including herpes simplex virus (HSV), can cause a keratitis. Therefore, it is important to find out if the infant's mother either tested positive or was symptomatic for HSV, rubella, or other pertinent infections during her pregnancy or delivery. Clinicians should obtain information about the infant's delivery because birth trauma, particularly the use of forceps to assist with delivery, can cause corneal lacerations, corneal edema, and clouded corneas. Care providers should review the family's detailed pedigree, which may reveal a genetic or familial inheritance pattern for the corneal clouding, which can help establish a metabolic or genetic diagnosis. Finally, physicians should conduct a thorough review of systems to identify any other coexisting congenital systemic anomalies that may provide clues to a syndrome unifying the ocular and systemic abnormalities.

When examining a newborn eye, it is important for the clinician to identify all the major structures of the anterior segment to recognize any potential abnormalities. In a normal eye (Fig 1), the cornea is clear and allows visualization of the structures posterior to it, namely, the iris and lens. Peripheral to the cornea is the white, opaque sclera which is covered by the conjunctiva. The limbus is the region where the sclera and cornea meet. Often, abnormalities in 1 segment of the eye occur in conjunction with abnormalities elsewhere in the eye. Therefore, it is critical to examine all the structures of the eye to identify all potential pathologies. The eyelids are particularly important when considering a corneal opacification. If a neonate has a defect in the eyelid, such as an eyelid coloboma, or a lagophthalmos, in which the eyelids cannot close fully, the infant is at risk for exposure keratopathy. In this situation, the infant's cornea can develop abrasions and ulcerations because the eyelid is no longer providing complete protection. The clinician should also note any lesions on the face and eyelid because this could assist with diagnosis. For instance, vesicles on the eyelids could signify a herpetic infection.

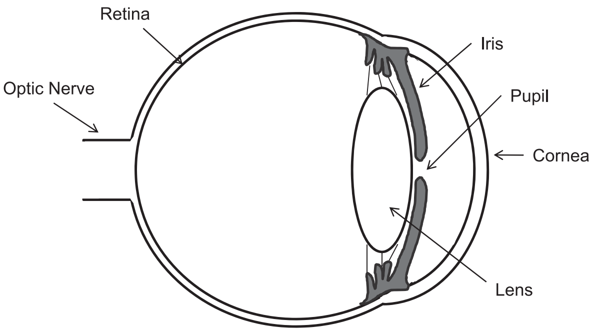

Figure 1. Anatomic structures of a normal eye.

The size of the eye is also important. A small eye (ie, microphthalmos), particularly one with many obvious ocular anomalies, could indicate a developmental problem with the eye in utero. In contrast, a large eye (ie, buphthalmos), with a larger than normal cornea, may suggest a diagnosis of congenital glaucoma. When examining the conjunctiva, the presence of conjunctival injection might suggest an inflammatory or traumatic component to the condition. In evaluating the newborn cornea, any opacification of the cornea is considered abnormal. Detailing the location of the opacification (central vs peripheral, anterior vs posterior) can help the clinician determine the diagnosis because various conditions can manifest in stereotypic patterns. Fluorescein staining at the bedside can be helpful if a corneal epithelial defect or herpetic infection is suspected. If it is possible to visualize the anterior segment despite the cloudy cornea, the clinician can inspect the iris to identify any iridocorneal adhesions, ectopic pupils, iris colobomas, or other structural abnormalities. Finally, the clinician can use a direct ophthalmoscope to evaluate the red reflex of the newborn eye to detect potential lens abnormalities such as cataracts as well as retinal abnormalities.

DIFFERENTIAL DIAGNOSIS

As mentioned before, there are various potential causes for congenital clouding of the cornea. The following is a mnemonic for the most common causes of congenital corneal opacification:

S – Sclerocornea
T – Tears in the Descemet membrane (from birth trauma or congenital glaucoma)
U – Ulcers
M – Metabolic
P – Peters anomaly
E – Edema (congenital hereditary endothelial dystrophy [CHED])
D – Dermoid

Congenital clouding of the cornea has many other rare causes, including cornea plana, corneal keloids, congenital hereditary stromal dystrophy, and oculoauriculovertebral dysplasia. For the purpose of this review, only the most common causes will be discussed further.

Sclerocornea

Sclerocornea is a rare congenital developmental abnormality of the eye. In this condition, intrauterine mesenchymal dysgenesis causes the cornea to become opaque, vascularized, and quite similar in appearance to the sclera, making the limbus indistinct (Fig 2). This disorder can have a spectrum of clinical findings, with milder cases having a clear central cornea. However, infants with severe manifestations can have near-total corneal involvement, though the central cornea is often still clearer than the periphery. This is in contrast to Peters anomaly wherein the central cornea is more opaque than the periphery. The corneal clouding found in infants with sclerocornea is full thickness through the stroma and will limit visualization of the intraocular structures.

Although sclerocornea is typically bilateral in occurrence, it can be unilateral in 10% of cases. It tends to occur sporadically but can have a familial or autosomal dominant inheritance pattern. Systemic associations include spina bifida occulta, cranial and cerebellar abnormalities, decreased hearing, limb deformities, cryptorchidism, Hallermann-Streiff syndrome, Smith-Lemli-Opitz syndrome, Mietens syndrome, osteogenesis imperfecta, and hereditary osteoonychodysplasias. The prognosis for severe cases of sclerocornea is guarded. Affected infants should be referred promptly for consideration of early corneal transplantation but often have quite limited visual potential despite surgical intervention.

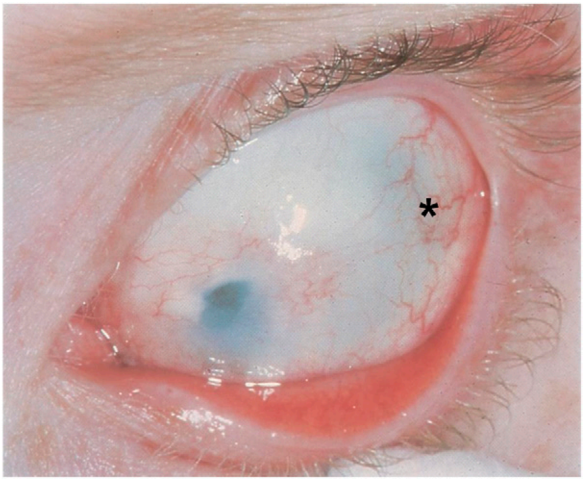

Figure 2. Scleral-like clouding of the cornea and corneal flattening in a child with sclerocornea. The asterisk (*) marks the indistinct limbus. (Adapted with permission, © 2015 American Academy of Ophthalmology, www.aao.org.)

Tears of the Descemet Membrane

The most posterior or innermost layer of the cornea is the endothelial cell layer (Fig 3). The Descemet membrane is a specialized basement membrane of the corneal endothelial cells that separates the posterior corneal stroma from the endothelial cell layer. The endothelial cells are responsible for actively pumping water out of the cornea and keeping it in a relatively desiccated state. If there is a tear in the Descemet membrane, the endothelial cell function declines and the cornea becomes edematous and thereby loses its clarity.

Traumatic injuries to the Descemet membrane are most commonly caused by forceps trauma to the eye during delivery. These tears are often vertical and linear in configuration. The rupture of the Descemet membrane leads to stromal, and occasionally, corneal epithelial edema, which in extreme cases can cause bullae or blisters on the surface of the cornea. Even after the corneal edema regresses, the edges of the torn Descemet membrane can persist and be visualized as ridges protruding from the posterior corneal surface. Often, other signs of trauma are apparent on the child's face and head as well. Infants may have periorbital soft tissue swelling or concurrent eyelid lacerations.

Descemet membrane tears are also common in congenital glaucoma. In this scenario, these tears are termed "Haab striae" and can be differentiated from traumatic Descemet membrane tears by typically being more horizontal and curvilinear in appearance. In addition, the eyes of affected infants will demonstrate higher intraocular pressures and often will have corneal enlargement and abnormally deep anterior chambers. It is critical to identify eyes at risk of having congenital glaucoma as early as possible because optic nerve damage from sustained ocular hypertension can cause permanent vision loss. These patients require surgery to address the glaucoma as soon as possible.

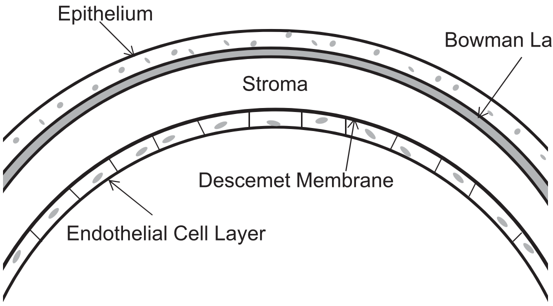

Figure 3. Layers of the cornea.

Ulcers

Viral keratitis, such as rubella or herpetic keratitis, can also produce a clouded cornea in a newborn. Herpes simplex infections most commonly occur in infants of women with active genital HSV infections. The risk of transmission is higher with a primary genital herpes infection than with recurrent activations of the virus. While most infants are infected during parturition, some may acquire the infection in an ascending manner after premature rupture of the amniotic membranes. Ocular involvement in congenital HSV infections most commonly consists of a blepharoconjunctivitis with vesicular eruptions on the eyelids and/or a keratitis with epithelial dendrites (branching treelike pattern of fluorescein staining on the corneal surface) that can be identified with fluorescein staining. It is important to perform a well-dilated funduscopic examination in these patients because some may have a chorioretinitis with vitritis and optic atrophy, particularly those with central nervous system involvement. Any infant who is suspected of having a herpetic keratitis should be promptly treated with systemic and topical antiviral medications because ocular disease often occurs in association with central nervous system involvement. The diagnosis can be confirmed by isolating the virus from vesicles or corneal scrapings if needed, using polymerase chain reaction and/or viral culture.

Corneal clouding associated with congenital rubella syndrome has dramatically decreased in incidence subsequent to the development and widespread usage of the attenuated rubella virus vaccine. However, the possibility of rubella should be considered in infants born to women who have not been vaccinated or who originate from developing countries where widespread rubella vaccination may not have been implemented. The corneal clouding in rubella syndrome can result from a true keratitis, or less commonly, an elevation of the intraocular pressure that leads to corneal edema. The associated keratitis often clears in weeks to a few months but residual scarring may persist. The most common associated ocular abnormalities in congenital rubella infection are cataracts and pigmentary retinopathy. Other systemic signs include sensorineural hearing loss, intellectual disability, hepatosplenomegaly, microcephaly, thrombocytopenic purpura, osteopathy, lymphadenopathy, and diabetes.

Metabolic Causes

Mucopolysaccharidoses. Mucopolysaccharidoses (MPSs) are lysosomal disorders that cause accumulation of glycosaminoglycans in various tissues. Affected children can present with corneal clouding as early as a few months of age that typically worsens with time. Corneal opacification is a prominent feature in all MPS I subgroups (Hurler, Scheie, Hurler-Scheie), MPS IV Morquio syndrome, and MPS VI Maroteaux-Lamy syndrome. Corneal clouding is not present in Hunter syndrome (MPS II) or Sanfilippo syndrome (MPS III). Although retinopathy can be found in patients with MPS, it is not often evident until children are at least several years of age, and may be obscured by the clouded cornea.

Sphingolipidoses. Typically, most sphingolipidoses affect the retina and spare the cornea except in Fabry disease. Fabry disease is inherited in an X-linked recessive pattern and can cause whorl-like opacities termed "verticillata" in the cornea epithelium. Other systemic signs of Fabry disease include skin lesions, peripheral neuropathy, and renal failure.

Mucolipidoses. Mucolipidoses, particularly GM gangliosidosis type 1 and mucolipidoses types I and III can manifest with corneal clouding as well.

Peters Anomaly

Peters anomaly is a central corneal stromal opacity, or leukoma, that results from a corneal defect affecting the posterior corneal stroma, Descemet membrane, and endothelium (Fig 4). Eighty percent of cases are bilateral, and 50% to 70% of affected infants also have glaucoma. One key distinguishing factor between the leukoma in Peters anomaly and other corneal clouding disorders, such as sclerocornea, is the lack of vascularization and the presence of a clear peripheral cornea. The defect may be accompanied by adherent iris strands (Peters anomaly type 1) or adherence of the lens (Peters anomaly type 2). The size and density of the corneal opacification can vary. In many cases, the central stromal leukoma can decrease in opacity with time. Peters

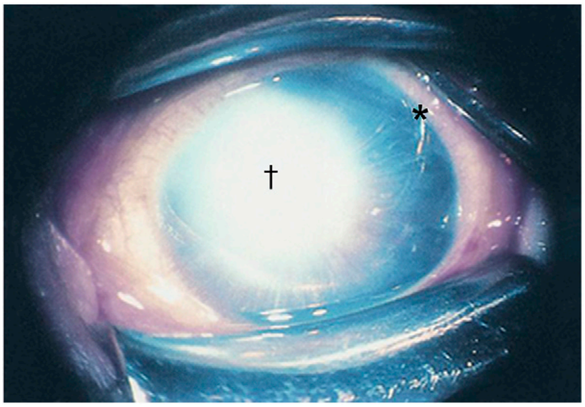

Figure 4. Central dense corneal opacity typical of Peters anomaly. The asterisk (*) symbol marks the limbus and the dagger (†) indicates the leukoma. (Adapted with permission, © 2015 American Academy of Ophthalmology, www.aao.org.)

anomaly can be caused by a multitude of diseases and genetic conditions such as Axenfeld-Rieger syndrome and congenital rubella. Unilateral cases are often isolated. However, bilateral cases can be associated with an underlying systemic disorder and should prompt a complete genetic evaluation. Systemic associations include craniofacial anomalies, congenital heart disease, pulmonary hypoplasia, syndactyly, ear abnormalities, genitourinary disorders, and central nervous system abnormalities. Peters plus syndrome is a rare autosomal recessive disorder with bilateral Peters anomaly, congenital brain defects, heart defects, and craniofacial abnormalities.

Edema (CHED)

CHED is a rare corneal dystrophy that manifests in infancy or early childhood with bilateral cloudy corneas, photophobia, tearing, and occasionally nystagmus. There are 2 types of CHED. In the type with an autosomal dominant inheritance pattern (CHED type I), the corneal haziness is progressive and often not detectible until the age of 2 years. However, in the type with an autosomal recessive inheritance pattern (CHED type II), the corneal clouding is present at birth and not progressive. Harboyan syndrome is a variant of CHED type II with the characteristic features of corneal opacification and edema at birth as well as sensorineural deafness.

Dermoids

Epibulbar or limbal dermoids are benign congenital tumors composed of choristomatous tissue (tissue derived from germ cell layers not normally found at that site). They often consist of fibrofatty tissue covered by keratinized epithelium and may contain hair follicles, sebaceous glands, or sweat glands (Fig 5). These tumors usually straddle the limbus and are most commonly found at the inferotemporal limbus. They can be very large, up to 10 mm in diameter, and can cause a lipoid infiltration of the corneal stroma at their leading edges. Large epibulbar dermoids can produce significant astigmatism with resultant amblyopia, and rarely, can cover the visual axis. Removal of these limbal dermoids is indicated if they cause amblyopia or ocular irritation, but residual scarring will be present. Epibulbar dermoids are most commonly isolated findings but 30% of cases are associated with Goldenhar syndrome (oculoauriculovertebral spectrum). Children with Goldenhar syndrome may have a myriad of other anomalies, including ear deformities and preauricular skin tags, eyelid colobomas, Duane retraction syndrome, maxillary or mandibular hypoplasia, and vertebral anomalies.

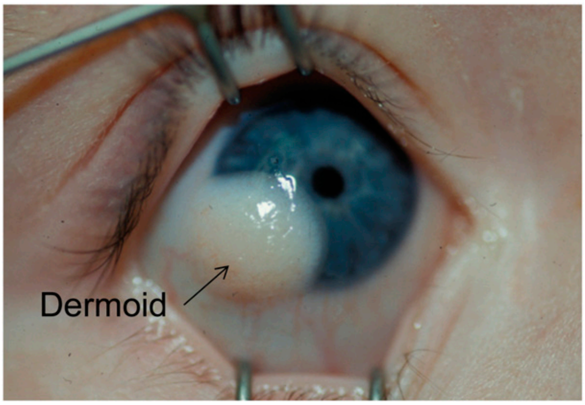

Figure 5. Limbal corneal dermoid. (Adapted with permission, © 2015 American Academy of Ophthalmology, www.aao.org.)

MANAGEMENT

The management of congenital corneal opacities in infants is challenging, and the approach must be tailored to the specific cause and child. Several factors must be considered when deciding on the best treatment strategy. First, the size and density of the corneal opacity is important in determining how much a patient's vision is affected. A larger peripheral opacity may not affect vision as much as a smaller, denser, central one that is overlying the pupillary axis. If the opacity is small and central, it is possible that dilation eye drops may be used therapeutically to enlarge the pupil; this will allow the patient to see around the opacity, especially early in life, to aid visual development. Alternatively, an optical iridectomy can be created surgically wherein another or larger pupillary opening is created to allow some visual stimulation to occur.

Another factor to consider is refractive error. Any abnormalities in the corneal shape or makeup can affect a patient's refractive error. As a result, even if a corneal opacity is peripheral and not in the visual axis, it can still cause significant visual compromise by inducing anisometropia (ie, a large difference in refractive error between the 2 eyes). Finally, amblyopia is also a serious concern. Visual deprivation amblyopia can occur from the opacity occluding the visual axis. Moreover, refractive amblyopia can occur from the anisometropia that develops. As a result, it is imperative that these patients be evaluated by a pediatric ophthalmologist quickly; delays in treatment can be detrimental to a patient's end visual potential.

In some disorders, such as Peters anomaly, observation may be the best course of action because many of these opacities will spontaneously improve with time. However, in large, dense central corneal opacities, the option of a corneal transplant, or penetrating keratoplasty, must be considered. Penetrating keratoplasties in neonates are technically demanding because of the reduced scleral rigidity and increased elasticity in the newborn eye. The risk of intraoperative complications is high. In addition, children have higher rates of graft failure than adults and may require multiple repeat keratoplasties. These patients are also at risk of developing postoperative cataract and glaucoma. In addition, most of these patients carry a high risk for amblyopia from large refractive errors and require eyeglasses or contact lens treatment with prolonged patching regimens. As a result, if a patient has a unilateral corneal clouding, care providers must have an extensive discussion with the parents about the time and commitment involved in caring for an infant with a corneal transplant and the limited visual potential expected. If the involvement is bilateral, the decision to intervene and treat (at least 1 eye) is clearer, because it provides the infant with some level of visual function.

CONCLUSION

Corneal opacities in a neonate, while rare, can pose significant morbidity to a child's visual function. In the immediate newborn period, it is essential that the neonatologist recognize the disorders that can cause rapid loss of vision if left untreated, such as congenital glaucoma, as well as those that can signify serious underlying systemic conditions, such as congenital HSV or rubella. The prognosis for many of these disorders is limited; however, early and prompt care coordinated by the neonatal team and ophthalmology can provide the infant with the best chance of obtaining good visual function.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the importance of corneal opacifications.

Suggested Readings

Ciralsky J, Colby K. Congenital corneal opacities: a review with a focus on genetics. *Semin Ophthalmol*. 2007;22(4):241–246

Huang C, O'Hara M, Mannis MJ. Primary pediatric keratoplasty: indications and outcomes. *Cornea*. 2009;28(9):1003–1008

Karadag R, Chan TC, Azari AA, Nagra PK, Hammersmith KM, Rapuano CJ. Survival of primary penetrating keratoplasty in children. *Am J Ophthalmol*. 2016;171:95–100

Kurilec JM, Zaidman GW. Incidence of Peters anomaly and congenital corneal opacities interfering with vision in the United States. *Cornea*. 2014;33(8):848–850

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Nischal KK. Genetics of congenital corneal opacification: impact on diagnosis and treatment. *Cornea*. 2015;34(suppl 10):S24–S34

Shigeyasu C, Yamada M, Mizuno Y, Yokoi T, Nishina S, Azuma N. Clinical features of anterior segment dysgenesis associated with congenital corneal opacities. *Cornea*. 2012;31(3):293–298

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1. You are performing a routine newborn physical examination and note a right eyelid coloboma. Which of the following concerns is most appropriate in the presence of this condition?
   - A. Herpetic or adenoviral infection.
   - B. Group B streptococcal sepsis.
   - C. Exposure keratopathy with risk of abrasion.
   - D. Congenital glaucoma.
   - E. No concern at present with almost certain likelihood of spontaneous resolution.
2. You are called to examine a newborn infant due to concern for an eye abnormality. The infant appears to have bilateral partially opaque corneas. The central corneas appear clear, while the peripheral corneas appear opaque and similar in appearance to the sclera, making the limbus appear indistinct in both eyes. Which of the following is the most likely diagnosis?
   - A. Sclerocornea.
   - B. Secondary herpetic infection.
   - C. Dermoid tumor.
   - D. Syphilitic infiltration.
   - E. Peters anomaly.
3. You are performing a physical examination on a newborn infant and note what appears to be a vertical, linear tear on the cornea. You suspect Descemet membrane tear. Which of the following is the most common cause of this condition?
   - A. Herpes simplex infection.
   - B. Ophthalmic antibiotic ointment adverse effect.
   - C. Primary gonococcal infection.
   - D. Traumatic injury associated with forceps use during delivery.
   - E. Congenital abnormality associated with trisomy 18.
4. A male infant is noted to have abnormal-appearing, coarse facial features as well as abnormal neurologic findings. A congenital metabolic disorder is suspected and eventually diagnosed. Corneal opacification is noted at 2 months of age. Which of the following is the most likely diagnosis?
   - A. Hunter syndrome (mucopolysaccharidosis type II).
   - B. Sanfilippo syndrome (mucopolysaccharidosis type III).
   - C. Noonan syndrome.
   - D. Medium-chain acyl-coenzyme A dehydrogenase deficiency.
   - E. Hurler syndrome (mucopolysaccharidosis type I).
5. An infant with corneal opacity is identified as having Peters anomaly and has bilateral occurrence of this condition. Which of the following aspects of management is appropriate for this patient?
   - A. Because this condition is highly associated with the development of malignancy, it is considered a pediatric ophthalmic emergency, and surgery should be performed as soon as possible.
   - B. Because this condition is most commonly associated with heavy maternal alcohol use, social work and child protective services should be involved early in this infant's care.
   - C. Depending on the degree of opacification, observation may be the best course of action because many of these opacities will spontaneously improve with time.

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D. Approximately half of the cases of Peters anomaly can be treated and cured with intraopthalmic injections of corticosteroids, as long as treatment is initiated within the first few weeks after birth.

E. If the corneal opacity is peripheral and not in the visual axis, it will not affect the patient's refractive error and therefore, does not require further evaluation other than close follow-up.

Corneal Opacities in the Neonate

Monica R. Khitri

NeoReviews 2018;19;e269

DOI: 10.1542/neo.19-5-e269

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Mandibular Distraction for Micrognathia in Neonates

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Education Gaps

1. Pierre Robin sequence (PRS) comprises the clinical triad of micrognathia, glossoptosis, and upper airway obstruction. The severity of micrognathia and airway obstruction among neonates with PRS varies. The evaluation of neonates with micrognathia is not standardized across neonatal units, which may result in delayed referral to and, therefore, delayed evaluation and care by appropriate specialists.
2. Airway management for neonates with PRS ranges from noninvasive airway support to surgical intervention for mandibular lengthening. The gold standard surgical intervention is mandibular distraction osteogenesis (MDO), the goal of which is to anteriorly reposition the mandible and tongue base away from the posterior pharynx to relieve upper airway obstruction. The ideal anatomic endpoint of mandibular distraction is not yet known.
3. Surgical intervention for treatment of upper airway obstruction in patients with PRS carries a risk of complications and long-term effects. With the introduction of MDO for PRS less than 2 decades ago, long-term clinical outcomes data with MDO are currently lacking.

Abstract

Pierre Robin sequence (PRS) comprises the clinical triad of micrognathia, glossoptosis, and upper airway obstruction, with a reported incidence of 0.5 to 2.1 per 10,000 live births. The mainstay of management involves prompt diagnosis of airway obstruction and airway management. The gold standard surgical intervention for management of symptomatic micrognathia is mandibular lengthening by distraction osteogenesis (MDO) to anteriorly reposition a retroflexed tongue and relieve obstruction. Although MDO is often successful in the short-term in relieving upper airway obstruction and/or avoiding the need for permanent tracheostomy, the long-term effects of MDO are not yet elucidated.

Objectives

After completing this article, readers should be able to:

1. Describe the initial diagnostic evaluation, airway analysis and evaluation, and necessary referrals for neonates with Pierre Robin sequence.

AUTHOR DISCLOSURE Ms Zimmerman, Drs Humphries, Roy, and Reid have disclosed no financial relationships relevant to this article. Dr Reid has disclosed receipt of lab royalties from Applied Biologicals, Inc., from sales of I CAL cells. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

HRQOL	health-related quality of life
MDO	mandibular distraction osteogenesis
PEBP	pre-epiglottic baton plate
PRS	Pierre Robin sequence
PSG	polysomnography
TLA	tongue-lip adhesion
UAO	upper airway obstruction

2. Describe the indications for and technical aspects of mandibular distraction osteogenesis (MDO), along with its complications.
3. Recognize the importance of appropriate patient selection for MDO.
4. Recognize the psychological and quality-of-life implications of MDO.
5. Identify treatment alternatives to MDO.

INTRODUCTION

Micrognathia is defined as a developmentally small mandible with markedly posterior positioning of the mandibular alveolus relative to the maxillary alveolus. (1) Micrognathia has an incidence of 1 in 1,000 births. (2) This condition presents with a broad clinical range of severity, from asymptomatic presentation to severe upper airway obstruction (UAO), the treatment of which involves airway stabilization with or without surgical intervention to lengthen the mandible (Fig 1).

Pierre Robin sequence (PRS) includes the clinical triad of micrognathia, glossoptosis (ie, posterior displacement of the tongue), and UAO. Though not typically described as part of the triad, cleft palate is frequently associated with PRS, which can compound difficulties with feeding and speech both in the short- and long-term. Micrognathia can be diagnosed with imaging during the prenatal period, while the PRS triad is identified at birth. (3)(4) The prevalence of PRS has been cited as being between 0.5 and 2.1 per 10,000 live births, with the highest incidence among whites and the lowest incidence among non-Hispanic African Americans. (5) Tongue base prolapse and UAO in PRS may result in feeding difficulty, failure to thrive, brain damage, and sudden death. (1)(3)(6)(7) Mortality in PRS has been cited to range between 2.2% and 26%, most commonly because of obstructive apnea and cardiac failure as a result of severe airway obstruction. (8)

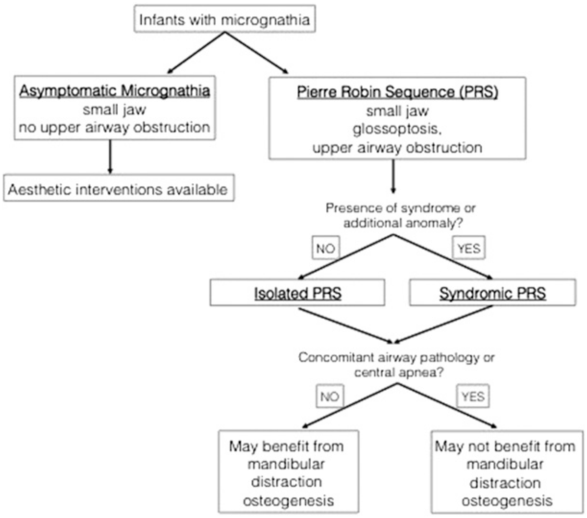
Infants with micrognathia
Asymptomatic Micrognathia
small jaw
no upper airway obstruction
Aesthetic interventions available
Pierre Robin Sequence (PRS)
small jaw
glossoptosis,
upper airway obstruction
Presence of syndrome or additional anomaly?
NO
YES
Isolated PRS
Syndromic PRS
Concomitant airway pathology or central apnea?
NO
YES
May benefit from mandibular distraction osteogenesis
May not benefit from mandibular distraction osteogenesis

Figure 1. Decision tree for evaluation and management of infants with micrognathia.

Furthermore, patients with PRS may be classified into "syndromic" or "isolated" groups. Patients with "syndromic PRS" have a concomitant syndrome or anatomic abnormalities. Syndromic PRS occurs in 45% to 80% of cases (Table 1). Patients with "isolated PRS" do not have other associated abnormalities. (3)(6)(8) Because of the frequent association with multilevel airway obstruction in syndromic PRS, achieving and maintaining an unobstructed airway in children with syndromic PRS tends to be more difficult than in children with isolated PRS. (3)

EVALUATION AND MANAGEMENT OF PRS

A systematic approach to the clinical evaluation and treatment of neonates with micrognathia is essential to provide comprehensive care (Fig 2). Asymptomatic micrognathia may require multidisciplinary input, but often, outpatient referral and follow-up are adequate. Alternatively, in a symptomatic patient with micrognathia and UAO, initial stabilization of the airway is an essential first step. Following stabilization, patients with micrognathia should undergo further evaluation to first establish whether the micrognathia is isolated or part of a syndrome. Patients identified as having PRS should undergo an extensive multidisciplinary evaluation that may include neonatology/pediatrics, sleep medicine, otolaryngology, plastic surgery, genetics, speech pathology, and nutrition services.

The primary objective of PRS treatment is securing a safe airway to improve oxygenation, and consequently improve feeding, speech, and developmental outcomes. Airway evaluation and stabilization should begin promptly

TABLE 1. **Common Syndromes Associated with Pierre Robin Sequence**

SYNDROME	INCIDENCE	ANATOMIC CHARACTERISTICS	PHYSIOLOGIC CHARACTERISTICS
Velocardiofacial syndrome	1:4,000 live births	Found in most patients with DiGeorge sequence and conotruncal anomaly face syndrome. Includes: Craniofacial anomalies • Retrognathia • Long face with prominent nose • Velopharyngeal weakness • Submucous or overt clefts Cardiovascular anomalies • Congenital heart defects • Carotid artery anomalies	Speech abnormalities (hypernasal) • Breathing difficulty • Chronic otitis media • Transient neonatal hypocalcemia • Mild intellectual impairment • Psychiatric disorders
Craniofacial or hemifacial microsomia (39)(40)	1:4,000–5,500 live births	A variable presentation including: Craniofacial anomalies • Mandibular hypoplasia • Microtia • Orbital distortion • Hypoplasia of facial muscles, parotid gland, and muscles of mastication Cardiac anomalies • Septal and outflow tract heart defects Goldenhar syndrome is within the spectrum of this disorder. Additional characteristics include epibulbar dermoids and vertebral defects	• Hearing impairment • Airway compromise
Stickler (41)(42) and Marshall syndromes (43)(44)	1:7,500–9,000 (Stickler)	Overlapping connective tissue disorders with: Craniofacial anomalies • Flat midface with depressed nasal bridge, short nose, anteverted nares • Micrognathia • May have soft palate cleft Eye anomalies • Abnormal vitreous gel in eye • Retinal detachment (Stickler) • Cataracts Musculoskeletal anomalies • Joint hypermobility • Arthritis • Osteoarthritis in 3rd or 4th decade • Spinal abnormalities • Spondyloepiphyseal abnormalities (Marshall) • Anhidrotic ectodermal dysplasia (Marshall) Cardiac anomalies • Mitral valve prolapse (Stickler)	• Airway compromise • Sensorineural deafness • Myopia
Treacher-Collins syndrome (45)	1:25,000–50,000 live births	Variable presentation but always bilateral. Includes: • Malar and mandibular hypoplasia • Zygomal cleft • Antimongoloid slanted eyes with eyelid notch (colobomas) • Retrusive jaw and chin • External ear abnormalities • Absence of eyelashes in medial third of lower eyelid • Cleft lip and choanal atresia may be present	• Conductive hearing loss • Airway difficulty and respiratory compromise • Speech and feeding difficulty

Continued

TABLE 1. **(Continued)**

SYNDROME	INCIDENCE	ANATOMIC CHARACTERISTICS	PHYSIOLOGIC CHARACTERISTICS
Nagar syndrome (acrofacial dystosis)(46)	Rare	Similar characteristics to Treacher-Collins syndrome, with noted differences • Absence of colobomas • Severe, wide cleft palate seen in all cases • Limb anomalies including hypoplasia of thumbs, radius, metacarpals • Short stature	• Hearing impairment • Secondary speech and language delays • Respiratory and feeding difficulty

after a diagnosis of PRS, beginning with conservative and noninvasive measures such as continuous pulse oximetry monitoring and prone or side positioning. Approximately 70% of patients can be stabilized with positioning changes alone. (8) (9) If repositioning does not adequately relieve obstruction, nasopharyngeal airway placement may be temporarily used for up to 2 to 4 months. Patients may also be treated with noninvasive continuous positive airway pressure therapy; however, large cohort data for its long-term effectiveness among patients with PRS are lacking. (10) Patients who fail less invasive airway support may require endotracheal intubation or even tracheostomy placement. If advanced airway support is required, or if patients demonstrate significant obstruction during oral feedings, nasogastric tube feedings may be necessary for nutrition. Genetic evaluation and neonatal screening in patients with PRS may identify the presence of concurrent congenital anomalies and syndromes (Table 1). A geneticist can help guide further evaluation. If more anomalies are identified, the infant may require additional evaluation by subspecialists (eg, neurology, cardiology, ophthalmology).

Polysomnography (PSG), or a "sleep study," determines the presence and severity of UAO and may identify

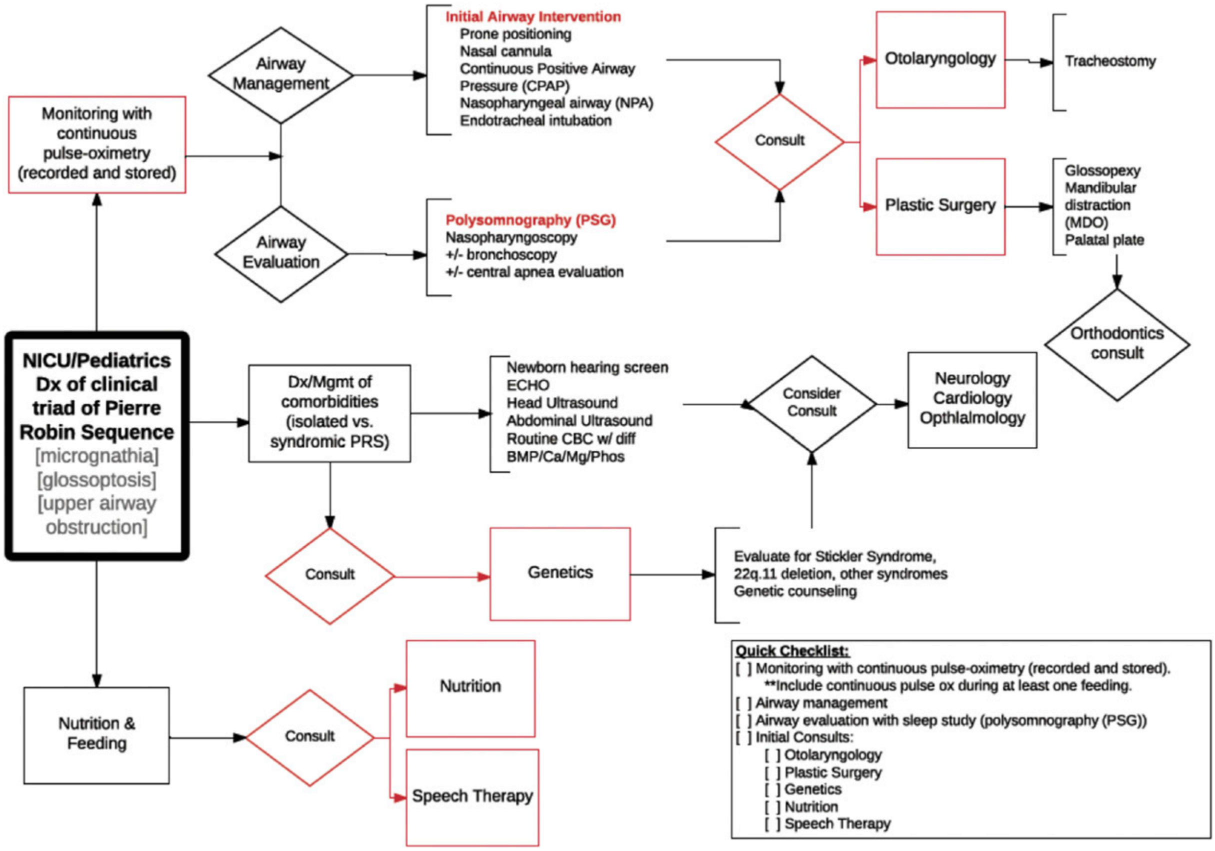

Figure 2. University of Chicago Hospital clinical evaluation and management guidelines for patients with Pierre Robin sequence (PRS). BMP=basic metabolic panel; CBC=complete blood cell count; ECHO=echocardiography.

concomitant central apnea by monitoring for specific respiratory events, including apneic and hypopneic events, and oxygen desaturations. The 2012 American Academy of Sleep Medicine guidelines delineate obstructive severity with an apnea-hypopnea index and with the lowest associated oxygen saturation (Table 2). (10)(11)(12)(13) Serial capillary blood gases with increasing carbon dioxide levels, respiratory acidosis with metabolic compensation, and oxygen desaturations at rest and during feedings can all support the diagnosis of chronic airway obstruction. (1)(3)(13)

Nasopharyngeal endoscopy should be routinely performed to identify concomitant upper airway pathology, including subglottic airway obstruction, which may occur in up to 23% of patients with PRS. (14) The identification of additional airway pathology is important, because its presence may influence the definitive management of PRS. (14)

Combining PSG and nasopharyngeal endoscopy results is useful to identify suitable candidates for mandibular distraction osteogenesis (MDO). Although the presence of central sleep apnea and/or concomitant airway pathology does not preclude the use of MDO to address UAO, patients may continue to have airway, breathing, and oxygenation problems given their comorbidities. Thus, patients with evidence of UAO on PSG with few or no central sleep apneas, along with absence of concomitant airway pathology may benefit the most from MDO.

SURGICAL MANAGEMENT OF PRS

Mandibular Distraction Osteogenesis

Although conservative noninvasive measures are typically effective to relieve airway obstruction, 23% of patients with PRS will require surgical intervention. (3)(8)(9) MDO has become the preferred surgical option at many institutions for neonates and infants with PRS-associated UAO who would otherwise require tracheostomy. (7)(15) MDO requires mandibular osteotomies and placement of distractors that allow for gradual lengthening of the mandible in an anterior-posterior direction. Anterior advancement of the mandible promotes anterior repositioning of the tongue relative to the oropharynx, with the goal of relieving tongue-based airway obstruction. McCarthy et al published the first clinical report of mandibular distraction with a rigid external distractor device for congenital mandibular deformities in 1992. (16) Since that time, both resorbable and nonresorbable internal distractor devices have been developed and are commercially available. (8)

The MDO process is invasive and the treatment regimen is intensive, spanning several weeks. The treatment involves an initial surgery to place the device, followed by a 3-phase distraction period. Figure 3 displays the authors' institutional timeline and protocol for the use of MDO in neonates. For neonates, the distraction period includes: 1) a latency phase, which is the 24-hour period after distractor placement and the start of distraction; 2) a distraction phase, wherein the anterior mandible segment is advanced a specific distance per day (typically 1 mm/day in a 0.5-mm twice-daily regimen), which may last up to 2 to 3 weeks depending on the rate of distraction and goal distraction length; and 3) a consolidation phase, a period ranging from 6 to 8 weeks after distraction completion to allow for bone healing. The devices are removed after the consolidation phase. (17)(18)(19)

At the authors' institution, PSG guides the endpoint of mandibular distraction. After the distraction phase of MDO is completed, PSG is performed to confirm resolution of the UAO. (20) The appropriate anatomic endpoint of mandibular distraction beyond the relief of UAO is unknown. While some advocate for overdistraction or "overcorrection" of the mandible, this practice may result in a severe underbite or class III malocclusion and have a long-term impact on maxillary-mandibular relationships. Recently, the concept of using airway volume and morphology to guide mandibular distraction endpoint was introduced. (15)(21) Preoperative virtual surgical planning using patient 3-dimensional computed tomography for skeletal reconstruction and soft-tissue airway volume calculations is useful and may serve as an objective adjunct in preoperative guidance and postoperative follow-up. (8) Figure 4 exhibits a clinical example.

TABLE 2. **Severity of Obstructive Sleep Apnea in Children (11)(12)(13)**

CATEGORY OF SEVERITY	APNEA-HYPOPNEA INDEX	MINIMUM OXYGEN SATURATION
Mild	<5	<90% for 2%–5% of sleep time
Moderate	5 to <10	<90% for 5%–10% of sleep time
Severe	>10	<90% for >10% of sleep time

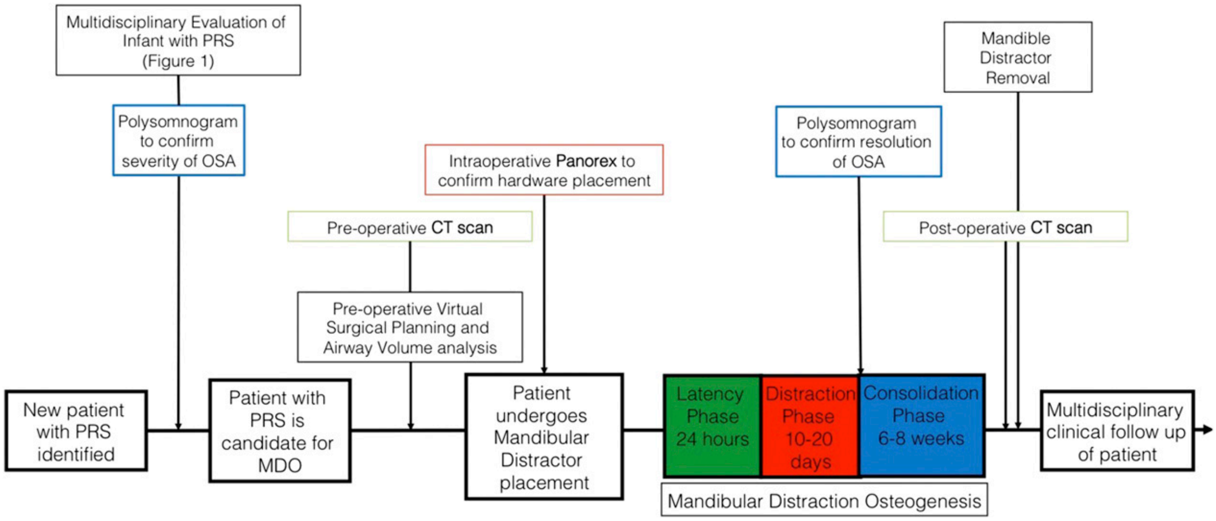
Multidisciplinary Evaluation of Infant with PRS (Figure 1)
Polysomnogram to confirm severity of OSA
Intraoperative Panorex to confirm hardware placement
Pre-operative CT scan
Pre-operative Virtual Surgical Planning and Airway Volume analysis
Polysomnogram to confirm resolution of OSA
Mandible Distractor Removal
Post-operative CT scan
New patient with PRS identified
Patient with PRS is candidate for MDO
Patient undergoes Mandibular Distractor placement
Latency Phase 24 hours
Distraction Phase 10-20 days
Consolidation Phase 6-8 weeks
Multidisciplinary clinical follow up of patient
Mandibular Distraction Osteogenesis

Figure 3. University of Chicago Hospital mandibular distraction osteogenesis timeline and protocol for patients with Pierre Robin sequence (PRS). CT=computed tomography; MDO=mandibular distraction osteogenesis; OSA=obstructive sleep apnea.

MDO OUTCOMES

Reported clinical outcomes of MDO are varied. Metrics include avoiding a tracheostomy or performing successful decannulation of the tracheostomy, meeting normal growth and developmental milestones, weaning from continuous positive airway pressure, and/or alleviating or significantly improving obstructive sleep apnea symptoms. Data compiled from systematic reviews and meta-analyses demonstrate that 82% to 100% of patients had an overall positive outcome from MDO. In particular, normal oral feeding was achieved in 86% to 100% of patients, and the axial skeleton growth curve normalized after 1 year in almost all cases. (8)(18)(22)(23) MDO is more likely to be successful in relieving UAO and result in tracheostomy avoidance in patients with nonsyndromic PRS compared with syndromic PRS with cognitive comorbidities; those with a syndromic condition with a disrupted mandibular growth center; and those without mandibular condyles, coronoid processes, or malformed glenoid fossas. (3) A previously mentioned literature review found a success rate of avoiding tracheostomy or achieving successful decannulation in 97.6% of patients with isolated PRS who underwent MDO compared with 94% in patients with syndromic PRS in subgroup analysis. (18)

High success rates from MDO depend on proper patient screening and selection. In addition to assessing for concomitant central sleep apneas and/or airway pathology with PSG and nasopharyngeal endoscopy, it is important to consider other systemic comorbidities that may affect MDO outcome. Specifically, if MDO is performed on patients with neurologic comorbidities, the surgery will not address underlying conditions such as chronic aspiration, hypotonia, and poor oral coordination, thus unnecessarily exposing the patient to surgical complications without achieving significant improvement in airway obstruction. (3)

MDO COMPLICATIONS

Short-term and long-term risks and complications associated with MDO are listed in Table 3. The overall complication rate of MDO is between 20.5% and 35.6%. (8)(17)(18)(24)

Commonly cited short-term complications include infection, inappropriate vectors of distraction (ie, direction or differential length of distraction between sides) resulting in malocclusion, device malfunction, fusion error (eg, premature bony healing or nonunion of bone segments), and nerve damage or palsy of the inferior alveolar nerve and/or the marginal mandibular nerve. The long-term complications attributable to MDO are not yet fully elucidated, but include malocclusion, relapse, tooth injury or abnormality, hypertrophic scarring, and limited mandibular range of motion. (1)(8)(17)(18)(24)(25) Data on complications include the following:

- Infections: Infections from MDO vary in their severity from superficial cellulitis to deep infections or osteomyelitis requiring device removal (incidence of 0.5%–0.9%). (24)
- Tooth abnormalities: The tooth-related injuries seen in 1.3% to 22.5% of patients are mainly caused by damage to unerupted molar buds during the MDO procedure. (24) A retrospective study of 10 infants with PRS treated with

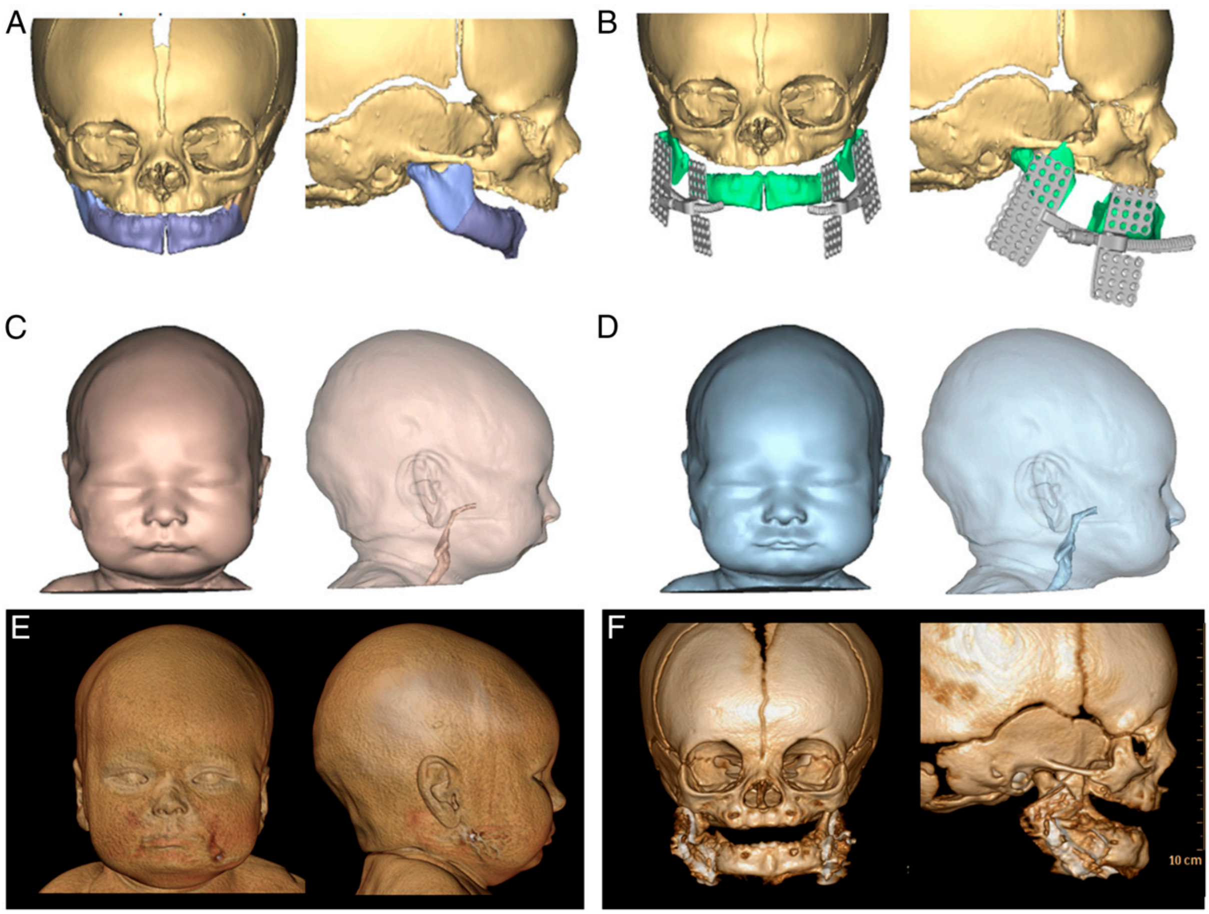

Figure 4. Clinical case. A 3-day-old female neonate with isolated Pierre Robin sequence (PRS), and wide Veau II cleft palate underwent multidisciplinary evaluation. She was found to have severe obstructive sleep apnea on polysomnography (PSG) (preoperative apnea-hypopnea index 35.91, nadir oxygen saturation high 80s), and deemed a surgical candidate for mandibular distraction osteogenesis. She underwent virtual surgical planning (VSP) preoperatively. A) Preoperative computed tomography scan with oblique orientation of mandibular osteotomies. B) VSP-calculated simulated placement of a 70-degree curvilinear distractor, with planned total advancement of 14.7 mm bilaterally. C) VSP-calculated preoperative airway volume (1,065 mm^3). D) VSP-simulated postoperative airway volume (1,497 mm^3) with planned mandibular distraction. At age 3 months and weight 3.0 kg, she underwent placement of the planned distractors. The latency phase was 24 hours, and distraction phase was 26 days with total mandibular advancement of 14 mm on the right and 10 mm on the left. Postdistraction PSG showed apnea-hypopnea index to be 2.6, and nadir oxygen saturation of 71%. The consolidation phase was 6 weeks. E) Soft tissue and F) bone changes after consolidation phase, before distractor removal.

MDO and followed for over 5 years demonstrated statistically significant position changes, shape anomalies, and root malformations of molars compared with matched controls. (22)

- Hypertrophic scarring: Hypertrophic scarring of the submandibular skin incisions, seen in 2.1% to 16.6% of patients, can necessitate scar revision. (1)(24) In 1 study, scar revision was recommended for 15% of patients. (3)
- Inferior alveolar nerve damage: The inferior alveolar nerve may be damaged during the MDO procedure and further aggravated by stretching during the distraction phase. Distraction rates over 1 mm/day are associated with a greater incidence of inferior alveolar nerve transient hypesthesia. (24)(26) There is a need for more investigation into the permanency of nerve damage from MDO.

There is some disagreement over whether relapse, defined as an increase in the sagittal overbite from its measurement immediately after MDO, should be considered a surgical complication or a normal postoperative phenomenon observed after MDO in skeletally immature patients with developmentally abnormal mandibles. (24) Relapse has been estimated to occur in up to 64.8% of patients who have undergone MDO. (24) Recurrence of significant UAO may require a second MDO procedure (~2.2% of patients) or tracheostomy placement for persistent obstruction (~2.2%). (18)

The ideal age at which to undertake MDO is worthy of discussion. It has been shown that MDO can treat patients

TABLE 3. **Rate of Complications Associated with Mandibular Distraction Osteogenesis**

SHORT-TERM COMPLICATIONS	LONG-TERM COMPLICATIONS
Infection	Malocclusion
• 6% (17)	• 2.4% (17) “skeletal open bite”
• 6.3% (18)	Relapse
• 9.5% (3)	• 64.8% (24)
• 11.8% internal nonresorbable, 12.8% external device, 18.5% resorbable (8)	Tooth injury/abnormalities
• 22% (25)	• 1.3% (18)
Inappropriate vector of distraction	• 21% (3) molar damage
• 0.67–8.8% (24)	• 22.5% (24)
Device malfunction	Scarring
• 1.5% (18)	• 2.1% (17)
• 2.9% internal nonresorbable, 6.4% external device (8)	• 2.3% (18)
• 7.3% (17)	• 15.6% (24)
• 7.5–7.9% (24)	Limited mandibular range of motion
Fusion error • 2.4% (24) premature consolidation and fibrous nonunion Nerve damage/palsy • 2% (25) • 2.5% (18) • 5.5% external device, 5.9% internal nonresorbable (8) • 11.4% (24)	• 1.1% (18)

with PRS who are only days old, but the smaller mandible size and lack of mineralization compounds the surgical complexity of distractor placement in this patient population. (27) One study found that patients older than 5 months had relatively fewer major postoperative complications; however, no statistically significant difference was found between overall complication rates in newborns and older infants. (27) Of note, adult patients have a worse prognosis after MDO, perhaps because of the reduced ability of adult mesenchymal stem cells to differentiate under the mechanical stress of distraction. (28)

Experience of the operating surgeon is another factor that affects MDO success. Surgeons who perform 10 or fewer craniofacial distractions per year have a complication rate as high as 55.6%, compared with the average 35.6% reported for MDO surgeries performed by experienced practitioners. (29)

MDO DEVICES—EXTERNAL AND INTERNAL

Mandibular distractors are available in 2 main categories: internal (Fig 4) and external devices (Fig 5). The most apparent difference between the external and internal distraction devices is their visibility and amount of facial obstruction. Internal devices, with no visible external hardware, have been cited to reduce parental anxiety, allow faster return to school or daycare, and facilitate breastfeeding. (8) (30) In addition, because the average distraction phase for internal devices is shorter, children undergoing internal distractor placement also experience reduced hospital length of stay. (8) Internal distractors have a lower risk of pin site–associated infections and by their nature, necessitate less wound care. The potential downside of internal devices is the inability to modify the vector of distraction after implantation; however, with virtual surgical planning and the ability to place internal devices more precisely, the aforementioned concern is mitigated. Both internal and external distractors require a second operation to remove the hardware, though on occasion, external distractors can be removed under sedation. Long-term injury of the marginal mandibular branch as well as greater hypertrophic scarring is cited more frequently with external distractors. Indications for the external distraction device have historically included the need for a multiplanar distraction and ability to immediately address mandibular asymmetries and open bite deformities during the surgery. To place internal distractors precisely, computed tomography is required, which necessitates additional radiation exposure. (1) However, in the last decade, the development of internal, multivector, and curvilinear models have facilitated a similar fine tuning of mandibular segments compared with that in the external models. (17)

A comprehensive literature review analyzing 711 pediatric patients younger than 18 years with craniofacial abnormalities who underwent MDO between 1992 and 2013 found that when distractor type was specified, a slightly higher percentage of internal distractors was used by surgeons (53.4% to 46.6%), particularly in more recent publications. The complication rate in this study was 22.1% with external distractors and 8.3% with internal distractors. (18)

POST-MDO MANAGEMENT

In light of the paucity of data on the long-term stability of MDO and the concern for tooth injury and long-term malocclusion, routine follow-up with dentistry, orthodontics, oral

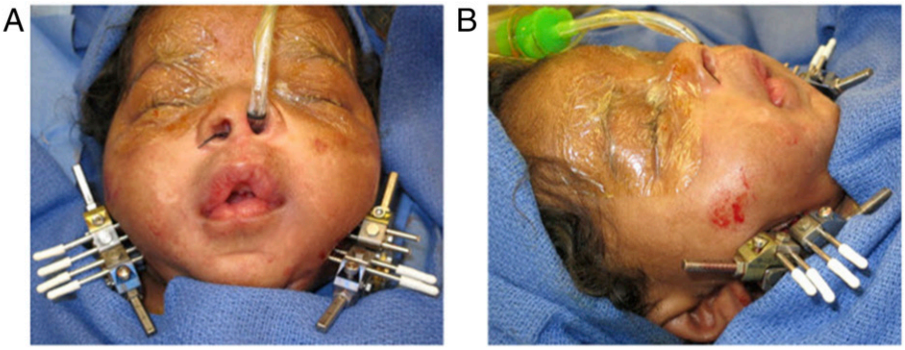

Figure 5. External mandibular distractors. Example of external mandibular distractor system in an 8-week old child with severe obstructive sleep apnea associated with Pierre Robin sequence. A) Frontal view; B) right lateral view.

surgery, plastic surgery, and otolaryngology is critical to achieve sustained success after MDO. As patients age after MDO, they may require further orthodontic care, aesthetic surgical procedures such as upper jaw or chin repositioning (genioplasty [cutting and repositioning the chin] or Le Fort osteotomy [cutting and repositioning the upper jaw]), and in some cases, repeat MDO. (1)(9)

At the authors' institution, patients with PRS with cleft palates typically undergo another PSG before cleft palate closure to ensure the absence of airway obstruction, because cleft palate repair, in and of itself, is pro-obstructive. (31) After cleft repair, these patients may develop abnormal speech because of velopharyngeal insufficiency leading to nasal air emission. (32) Some of the abnormal speech processes observed include hypernasality, hyponasality, velopharyngeal hypodynamism (functional impairment of the velopharyngeal apparatus), and replacement of oral sounds with glottal stop (consonant sound formed by air escape after closed glottis) or pharyngeal fricatives (sound formed by constricting airflow in the pharynx). (33) In these cases, early intensive speech therapy is recommended to correct these issues. Children as young as 1 year old can begin performing exercises to strengthen their velopharyngeal muscles. If speech therapy alone is insufficient, surgical interventions should be considered, including enlargement of the posterior pharyngeal wall, pushback palatoplasty to lengthen the palate, and pharyngeal flaps. (32) In addition, children with cleft palates are at increased risk for otitis media leading to conductive hearing loss. (34) Some institutional protocols suggest a hearing assessment every 6 months for patients between 1 and 4 years of age as well as otoscopic assessment for otitis media. Children with conductive hearing loss may benefit from insertion of tympanostomy tubes. (34)

MDO—QUALITY OF LIFE IMPLICATIONS

The term "health-related quality of life" (HRQOL) describes a metric that allows objective evaluation of a treatment's impact on the physical, psychological, and social aspects of a patient's day-to-day life. HRQOL is an important factor to include in the outcome metrics of a particular treatment. A survey study given to caregivers of children who previously underwent MDO demonstrated a benefit in HRQOL after MDO. (35) Caregivers felt that MDO provided the largest benefit in the physical domain, specifically the profile of the lower face. (35) Generalizability of these data is limited, given the small sample size (n=21) and retrospective nature of this study (with a time gap of 1–4 years). Thus, additional data are needed on the HRQOL benefit of MDO compared with other PRS interventions in children. In contrast, data from an HRQOL study on adult patients undergoing MDO in France showed that 43% of patients found the treatment painful, 19% of patients felt some degree of stress during the course of the procedure, and 17% of patients experienced sleep alterations. Patients were better able to persevere through treatments when they had hope for improvement. (36)

SURGICAL ALTERNATIVES TO MDO

Tracheostomy

Tracheostomy has been described as the definitive treatment for correcting UAO and is considered when other options fail, in cases of underlying neurologic conditions causing central apnea, or in cases of subglottic obstruction. Tracheostomy is a necessary treatment in approximately 10% of patients with PRS. (9) In some cases, a tracheostomy is used as a temporary measure with the goal of decannulation after the child grows and develops. Tracheostomies are associated with a morbidity of 43% to 65%, mortality of up to 6%, and the need for skilled nursing care and additional medical equipment at home. Complications associated with tracheostomy use include accidental decannulation or mucous plugging leading to sudden UAO, airway infections, bleeding, stomal maintenance problems, speech and swallowing delay, granulations, and laryngeal/tracheal stenosis. (3)(8)(37)

Tongue-Lip Adhesion

Tongue-lip adhesion (TLA) is a variant of the glossopexy procedure. It involves releasing the genioglossus muscle of the tongue in an attempt to bring the tongue forward and open the pharyngeal airway to relieve UAO. The TLA is typically released by 12 months of age. Although this procedure works well for managing UAO, it tends to exacerbate dysphagia. Children often have difficulty maintaining adequate nutritional intake with this procedure and may require prolonged nasogastric or gastrostomy tube feedings. Over 80% of institutions have stopped using this procedure, turning more toward alternative methods of nasopharyngeal airway stabilization. (3)

NONSURGICAL ALTERNATIVES TO MDO

Given the morbidity associated with surgical treatment of UAO, there is great interest in developing nonsurgical alternatives to relieving the obstruction, particularly when conservative measures such as prone positioning, nasopharyngeal intubation, and continuous positive airway pressure are inadequate. Nonsurgical treatment of UAO in patients with PRS should be aimed at pharyngeal wall stabilization and hypopharynx widening by shifting the tongue anteriorly to attenuate the effects of glossoptosis.

In Germany, several studies have demonstrated success with the use of a removable orthodontic pre-epiglottic baton plate (PEBP) with a velar extension to treat PRS-associated UAO (Fig 6). The device is custom made from a patient maxillary cast model and is composed of compound soft and hard acrylic. The device covers the palate and the alveolar ridges and contains a velar extension, the position of which is modified under endoscopy. (6) The device is held in place with suction adhesion, and sometimes requires the addition of an external wire structure to be secured via adhesive to the patient's face.

In patients with isolated UAO who underwent preintervention PSG, the use of a PEBP device significantly improved mixed-airway obstruction index scores 3 months after application without adverse effects. (38) In many infants, the use of a PEBP not only significantly improves UAO, but with reliable therapy, also promotes sucking and feeding without significant morbidity compared with a similar device without velar extension. (6) By stimulating weight gain and improving overall nutritional status, the use of PEBP in this patient population may obviate the need for supplemental enteral nutrition.

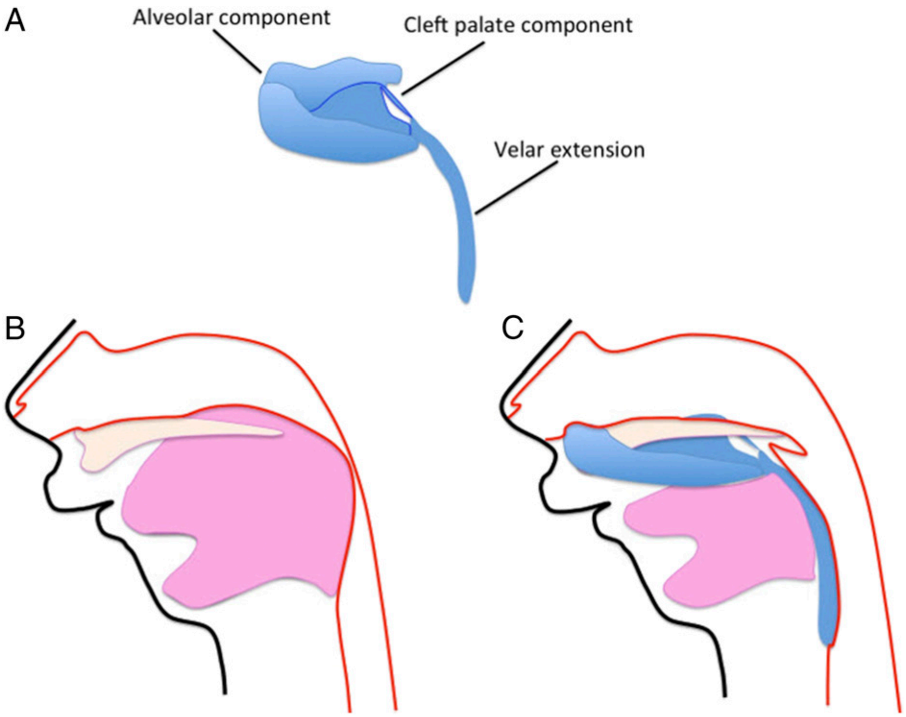

Figure 6. Pre-epiglottic baton plate (PEBP) with velar extension. A) Diagram representation of the PEBP with velar extension, with each of the alveolar, cleft palate and velar extension components. B) Diagram of a patient with Pierre Robin sequence (PRS), including micrognathia, glossoptosis, cleft palate, and posterior oropharyngeal narrowing. C) Diagram of PEBP with velar extension demonstrating anterior repositioning of posterior tongue base in a patient with PRS, thus increasing the posterior oropharyngeal space.

By precluding the need for prolonged general anesthesia and surgical intervention, such as tracheostomy and MDO, the use of PEBP is an attractive option to address isolated UAO in patients with PRS. Although data from the German experience are promising, the use of PEBPs has not yet been described in the United States.

CONCLUSIONS

Standardized clinical evaluation and management guidelines in pediatric units and NICUs are essential to ensure timely diagnosis, evaluation, and management of UAO in patients with micrognathia and in those with PRS. Specifically, a multidisciplinary care team is required to ensure that patients receive proper airway evaluation, necessary surgical treatments, genetic consultations and subsequent referrals, and continuous nutrition and speech therapy. We herein present a flow management algorithm to aid in identifying and treating patients with PRS.

MDO remains the gold standard surgical treatment available to definitively relieve UAO in select patients with PRS. However, it carries morbidity and risk in both the early and late postoperative period. The exploration of less invasive treatment options, such as the PEBP with velar extension, may avoid the risks and complications associated with surgical intervention in a subset of patients with PRS.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the associations and clinical features and management of macroglossia and hypoplastic mandible, including the Pierre Robin syndrome.

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1. A newborn patient presents with the clinical triad of micrognathia, glossoptosis, and upper airway obstruction (UAO) and is identified as having Pierre Robin sequence (PRS). The incidence of PRS varies by race and ethnicity and has been found to be highest in patients with which of the following background?
   - A. Asian/Pacific Islander.
   - B. White.
   - C. African American.
   - D. American Indian/Alaska Native.
   - E. Hispanic.
2. The newborn patient with PRS has signs of respiratory distress including grunting and subcostal retractions. The primary objective of PRS treatment is to secure a safe airway beginning with conservative and noninvasive measures such as continuous pulse oximetry monitoring, and prone or side positioning. What is the proportion of infants that can be stabilized with positioning changes alone?
   - A. 10%.
   - B. 25%.
   - C. 50%.
   - D. 70%.
   - E. 90%.
3. The newborn patient with PRS has been stabilized and management plans are being discussed with the parents. Mandibular distraction osteogenesis (MDO) has become the preferred surgical option at many institutions for neonates and infants with PRS-associated UAO. The treatment involves an initial surgery to place the device, followed by a 3-phase distraction period that includes a latency phase, a distraction phase, and a consolidation phase. Which of the following statements regarding MDO is CORRECT?
   - A. During the distraction phase, the mandibular segment is typically advanced by 1 mm daily.
   - B. The latency phase is typically is a 48- to 72-hour period after distractor placement and before the start of distraction.
   - C. A 12-week consolidation phase is necessary to allow for complete bone healing.
   - D. Mandibular distraction is considered complete once the mandible is advanced beyond a standardized anatomic endpoint.
   - E. Overcorrection of the mandible is recommended to ensure appropriate relief of the UAO.
4. The patient with PRS is preparing for the MDO procedure. While data from systematic reviews and meta-analyses indicate that 82% to 100% of patients have an overall positive outcome from MDO, short- and long-term complications have been described. Which of the following statements is CORRECT regarding MDO complications?
   - A. The overall complication rate of MDO is 10%.
   - B. Osteomyelitis requiring device removal is the most common infection following MDO with an incidence of 1.8%.
   - C. The tooth-related injuries seen in as many as 22.5% of patients are mainly caused by damage to unerupted molar buds during the MDO procedure.
   - D. Hypertrophic scarring of the submandibular skin incisions is uncommon, occurring in less than 1% of patients.
   - E. Inferior alveolar nerve damage only occurs in overaggressive distraction rates over 1.5 mm/day.

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5. A newborn patient with PRS is noted to have evidence of UAO. Various surgical and nonsurgical options are available for patients with UAO not responding to position changes alone, including tracheostomy and the tongue-lip adhesion (TLA) procedure. Which of the following statements is CORRECT regarding these alternative methods of treatment?
    - A. A tracheostomy is a necessary treatment in approximately 25% of patients with PRS.
    - B. Tracheostomies are associated with mortality rates as high as 10%.
    - C. The TLA procedure works well for managing UAO, but is no longer performed in a majority of centers because of the high incidence of feeding difficulties associated with it.
    - D. The TLA is typically released by 6 months of age.
    - E. A custom-made orthodontic pre-epiglottic baton plate has been shown to improve UAO but is associated with poor feeding outcomes.

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Videolaryngoscopy for Intubation Training

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Education Gaps

1. The best way to train residents, fellows, and inexperienced laryngoscopy operators remains to be determined. Videolaryngoscopy provides an effective method for training inexperienced operators and improves the learning curve for safe endotracheal intubation in neonatal and pediatric patients. More frequent use of the videolaryngoscope in the early stages of training provides many advantages for short- and long-term clinical proficiency.
2. For a known or suspected difficult airway, one should ensure basic preparation such as identification of backup strategies for intubation, as well as preparing all potentially necessary equipment for managing the difficult airway. At a minimum, it is strongly recommended that a videolaryngoscope should be available in these scenarios.

Abstract

Intubation in the neonate can present unique challenges to an inexperienced clinician. The videolaryngoscope provides more easy visualization of the airway, as well as more reliable access to the airway. Since its inception, the videolaryngoscope has been modified from its original adult design for use in the pediatric patient population. Following its production, one of its main uses has been in the training of inexperienced operators, gaining widespread use in training hospitals. Before its introduction, instructors at these institutions relied solely on feedback from the trainee during intubation, rather than visual confirmation. Use of the videolaryngoscope to instruct trainees on the technique of intubation improves feedback given to the trainee as well as the first-attempt success rates, while lowering esophageal intubation rates. The available literature suggests that the use of videolaryngoscopy improves visualization of the glottis while sacrificing time to pass the endotracheal tube. Both methods (direct and videolaryngoscopy) proved to have similar times for intubation as well as intubation success rates for experienced practitioners. In the neonatal and pediatric populations specifically, another crucial use of videolaryngoscopy is its superiority in treating patients with a difficult airway. It enhances the operator's ability to visualize the glottis in cases with no direct line of sight to the glottis.

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ABBREVIATIONS

DL	direct laryngoscopy
LCD	liquid crystal display
VL	videolaryngoscopy

Objectives After completing this article, readers should be able to:

1. Understand how the funnel-shaped infant airway presents unique challenges to endotracheal intubation in comparison to its adult counterpart. Difficulty achieving an adequate glottal view using traditional direct laryngoscopy blades may be as high as 37%.
2. Consider how the use of a videolaryngoscope improves the quality of feedback given to trainees, improves first-attempt success rates, and lowers the risk of esophageal intubation.
3. Describe how the 60-degree angle of the videolaryngoscope blade provides improved glottal visualization without requiring direct line of sight.
4. Consider that even for the experienced laryngoscope operator, the videolaryngoscope should always be available for a difficult airway.

INTRODUCTION

Tracheal intubation is a lifesaving procedure and is an essential step in elective general anesthesia and cardiopulmonary resuscitation. (1)(2) In pediatrics, intubation presents unique challenges for trainees because the airway is considerably different from the adult airway, and obstruction of the airway can lead to rapid cardiorespiratory decompensation in infants and children. (3)(4)(5) Specific to the neonate, a more cephalad larynx, a narrower epiglottis, a relatively larger tongue, larger occiput, and a more limited mouth opening contribute to increased difficulty for laryngoscopy and intubation. (1)(2)(3)(5)(6)(7)(8) One study used video bronchoscopy in anesthetized and paralyzed children to measure the cross-sectional area of the airway at the level of the glottis and the cricoid. Their findings suggested that the glottis, rather than the cricoid, is the narrowest portion of the pediatric airway. (9) However, a more recent autopsy study confirms that the infant larynx is funnel-shaped with the narrowest portion found at the near-circular nondistensible cricoid cartilage. (10)

Before the development of videolaryngoscopy (VL), endotracheal intubation of the neonate was uniformly performed via direct laryngoscopy (DL). Typically, DL operators in the NICU use a Miller blade, sized 00 to 1, depending on the infant's size, to visualize the airway and pass the endotracheal tube into the trachea. Although conventional DL is usually rapid and atraumatic in experienced hands, the difficulty in obtaining glottis exposure with traditional DL blades may occur in as many as 37% of cases. (11) In this review, the authors aim to assess the advantages of VL in the neonatal and pediatric populations, focusing on how this technique addresses 2 essential clinical issues in the neonate: the instruction of trainees and the management of the difficult airway.

THE UTILITY OF VL FOR INSTRUCTION OF TRAINEES

Before the advent of VL, instructors relied mainly on feedback from the trainee during intubation, rather than visual validation. (1)(2)(3) Because of the low pulmonary reserve and high oxygen consumption in small infants, instructors were often unable to correct trainees using real-time feedback when problems arose during DL for fear of the infant experiencing rapid decompensation. (8)(11) Instead, instructors found it necessary to perform endotracheal intubation themselves, delaying the achievement of trainees' competence in endotracheal intubation. (8)

With this issue in mind, extensive research went into developing pediatric VL devices to better visualize the oral and pharyngeal axes, providing a better view than that available with DL visualization. (1)(3)(5) These VL devices provide high-resolution cameras and liquid crystal display (LCD) monitors to improve the view of the laryngeal inlet independent of the direct line of sight. (3)(4)(5)(8) Traditional DL relies on direct line of sight of the glottal channel. To achieve this direct line of sight, maneuvers including neck flexion, head extension, and laryngeal depression, all stimulating and sometimes dangerous maneuvers, may be required. In 2001, Dr Jack Pacey, a Canadian vascular surgeon, invented the adult GlideScope videolaryngoscope. It was designed to provide a more reliable and more easily achieved visualization of and procedural access to the airway (Fig 1). Later, in 2005, a miniaturized pediatric GlideScope was introduced. Today, anesthesiologists, intensivists, emergency medical services, and military teams around the world use the GlideScope videolaryngoscope routinely.

The videolaryngoscope handle is similar to that of a standard laryngoscope. A wide-angling video camera, along with 2 light-emitting diodes placed on either side of the camera to provide illumination, is placed on the tip of the blade in combination with an antifogging device. (7) The image captured by the camera is displayed on an LCD monitor, resulting in improved glottic visualization. (1)(3)(4)(5)(7) In contrast to the standard laryngoscope, the blade is not detachable and has a 60-degree anterior curvature in the midline. (3)(5)(7) The 60-degree angle of the blade provides improved visualization without requiring alignment of the oral, pharyngeal, and tracheal axes. It also does so without requiring any additional lifting force. (5)(7)

Since their introduction, neonatal and pediatric videolaryngoscope blades have evolved through several generations. After the GlideScope, other videolaryngoscopes were developed, including the C-MAC® (Karl Storz, Tuttlingen, Germany), a system offering the familiarity of the Macintosh standard laryngoscope blade; the TruView PCD (Teleflex, Wayne, PA), which offers a magnified laryngeal view; and the McGrath MAC (Medtronic, Minneapolis, MN), which gives the laryngoscope operator the option to use the device as a standard or videolaryngoscope. (6)(12)(13)(14) Figure 2 shows a comparison of these various laryngoscope blades. Bearing in mind the differences among pediatric videolaryngoscopes, this review will focus on the use of the pediatric GlideScope.

Research evaluating laryngoscopes and alternative intubation devices has historically focused on improving laryngeal exposure. As 1 of these "alternative devices," the videolaryngoscope allows the operator to "look around the corner." With the various angles provided, the individual intubating the airway can extend his or her line of sight beyond a large tongue, small mandible, retroflexed epiglottis, or hypopharyngeal soft tissue crowding. When a direct line of sight of the glottis is encumbered during DL, the view can be achieved with the videolaryngoscope, thus leading to successful intubation. This improvement results from the lighting and video technology at the tip of the laryngoscope capturing an image, which is then projected onto a screen that is easily viewed by the operator.

Several studies have compared the use of video-assisted laryngoscopy to traditional laryngoscopy in the pediatric population. Most have found no difference in time to intubate and intubation success rates for experienced operators; however, VL did improve the view of the glottis while sacrificing time to pass the tube. (1)(5)(15) Recently 2 Cochrane reviews examined VL versus traditional DL. The first study was conducted in neonates, and the second looked at the pediatric population excluding neonates. In the systematic review of the neonatal population, the

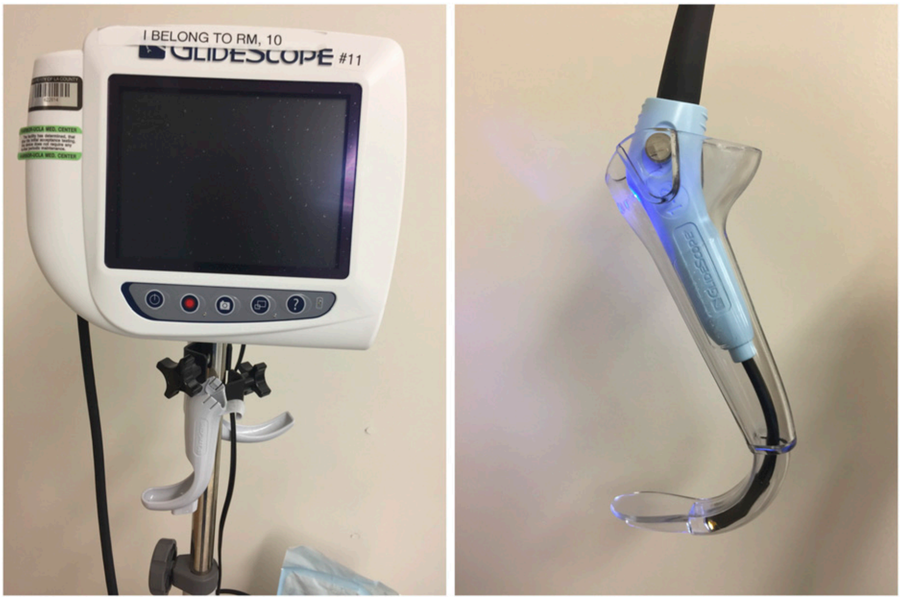

Figure 1. GlideScope videolaryngoscope. Left panel shows GlideScope liquid crystal display screen for monitoring the laryngeal inlet during endotracheal intubation. Right panel shows curved laryngoscope blade (clear cover) with internal light and video components.

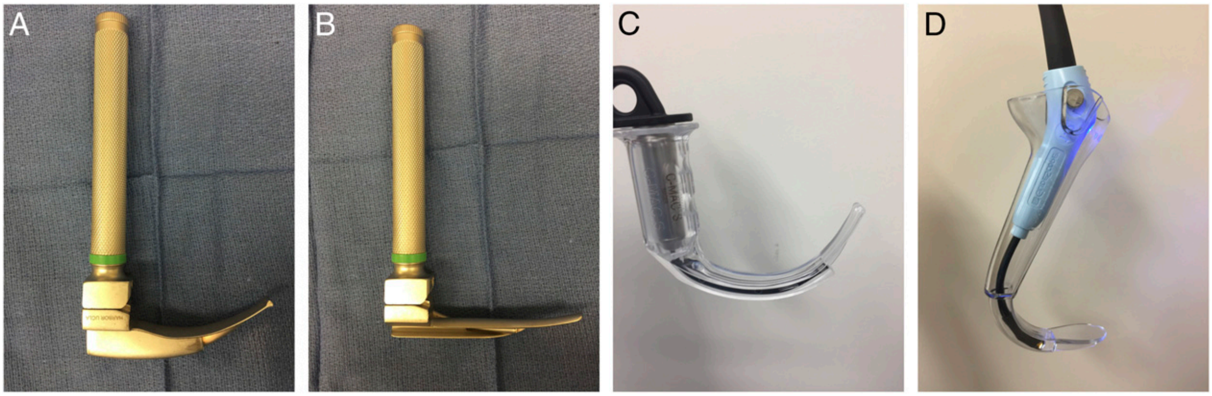

Figure 2. Laryngoscope blades. A and B depict the Macintosh and Miller blades for traditional direct laryngoscopy, respectively. C and D depict the videolaryngoscope blades of the C-MAC® and the GlideScope, respectively.

researchers attempted to evaluate the efficacy and safety of VL compared with DL in decreasing the time and number of attempts at intubation while increasing success rate. Ultimately, they found that there is insufficient evidence in the literature to recommend the use of a videolaryngoscope in either the NICU or the delivery room. In contrast, in the Cochrane review of a pediatric population, Abdelgadir et al noted that, when excluding neonates, VL led to prolonged intubation times and an increase in the rate of intubation failure compared with traditional DL. (16) All of the aforementioned studies focused on children and neonates with normal anatomy in whom intubation was performed by an expert. (2)(16)

However, in contrast to these findings, VL appears to offer an advantage in specific cases in which airway visualization fails because of operator inexperience. Not only does the videolaryngoscope provide an enhanced view of the glottis to the laryngoscope operator (Fig 3), but it also provides the same view to observers in proximity to the operator, who may be supervising or providing additional expert opinion on the safe establishment of an endotracheal airway. The use of VL, therefore, presents the perfect opportunity to improve upon traditional methods of teaching the procedure of intubation (Fig 4).

A few studies have examined the use of VL in teaching residents to perform intubation in patients. Sakles et al investigated the use of VL for teaching trainees in the emergency department of an academic institution. (17) In 2014, they published a study evaluating emergency medicine residents' (postgraduate years 1–3) intubation performance using VL or DL. They found that, across all trainee years, the residents had an increase in first-pass intubation success using VL compared with DL. In addition, they noted that, as the individual resident's training progressed, he or she improved significantly using VL but not using traditional DL. (17) In 2015, Sakles et al published another emergency medicine study concluding that the use of VL in training emergency medicine residents to perform intubation significantly lowered their rate of esophageal intubation. (18) Both of these studies were conducted in an academic emergency department where the patient population predominantly comprised adults.

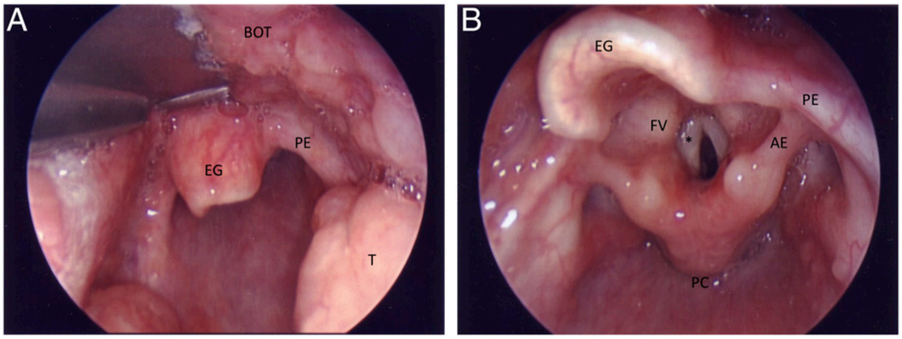

Figure 3. Videolaryngoscopic versus direct laryngoscopic views of the difficult airway, in a 16-month-old girl with a history of difficult intubation. A, view of the glottis using a Miller 1 laryngoscope. Note poor control and retroflexion of the epiglottis obscuring view into the glottal inlet. B, view of the glottis using the GlideScope videolaryngoscope. AE=aryepiglottic fold; BOT=base of tongue; EG=epiglottis, FV=false vocal fold; PC= postcricoid; PE= pharyngoepiglottic fold; T= palatine tonsil; *=true vocal fold.

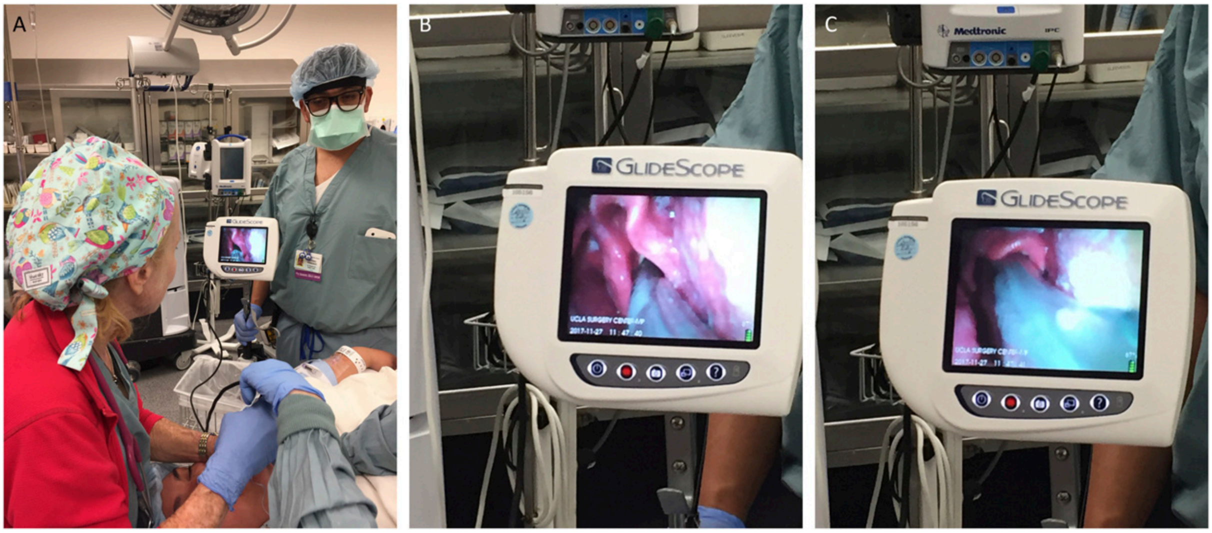

Figure 4. Team use of GlideScope videolaryngoscopy. A, an experienced anesthesiologist using the GlideScope to perform intubation in a morbidly obese 16-year-old patient. The anesthesiologist is surrounded by trainees who are shown her view of the airway. The trainees observed the anesthesiologist pass the endotracheal tube on the first attempt. B and C demonstrate the view of the successful endotracheal intubation.

So, how do these findings in adults translate to the pediatric population? Koele-Schmidt and Vasquez conducted a study teaching intubation to postgraduate year 1 residents rotating in the NICU at an academic hospital. (19) Trainees were taught intubation using 3 methods: traditional bedside DL, VL, and a computer-training module. During the exercise, the trainers found that the residents were faster at performing intubations using the direct laryngoscope. However, when surveyed after the training exercise, the residents endorsed that, although only 33% preferred using VL to DL, 76% thought that VL was a superior training method. (19) Other studies have shown similar feedback from trainees, and some have shown that proficiency at pediatric intubation using VL translates into improved aptitude in intubation using DL. As such, physicians early in their training, learning how to perform intubation in pediatric and/or neonatal patients, should routinely use VL when available. It is safer and improves their early successes, instilling the necessary skill set and confidence going forward.

THE UTILITY OF VL IN MANAGING DIFFICULT NEONATAL AIRWAYS

A few studies have examined intubation in children with a difficult airway or challenging anatomy. Figure 3A provides an example of more difficult airway anatomy with a large base of the tongue, crowded oropharynx, and a retroflexed epiglottis. Burjek et al compared the use of flexible fiberoptic intubation with VL-assisted intubation in the difficult pediatric airway and found that the flexible bronchoscope provided a superior view of the glottis compared with the videolaryngoscope. (20) They also found that the ability to ventilate during bronchoscopy led to a reduction in hypoxemic events during intubation. (20) Vlatten et al performed a randomized controlled trial assigning patients with difficult anatomy to either a VL or a DL group for intubation. (21) They found that, in children with abnormal anatomy, experienced anesthesiologists achieved a superior view of the glottis with VL, but it ultimately took them longer to pass the tube and intubate when compared with DL. (21) On the other hand, when evaluating inexperienced anesthetists, it has been shown that using VL improves their success rate and shortens their time to intubation. (22) Therefore VL is the preferred choice for intubation of a difficult airway by a less experienced operator. It may become the preferred choice for experienced operators also as its use becomes more widespread and routine.

CONCLUSION

Although the primary implementation of the videolaryngoscope was to provide a superior view of the larynx during intubation, it appears that the true power of this tool lies in its unrivaled mechanism of teaching trainees and novice operators the technique of endotracheal intubation. Along the same vein, the literature suggests that for inexperienced operators, VL may be helpful as the primary avenue for managing difficult neonatal airways. Every new device has a learning curve. VL has the capacity to steepen the learning curve for novice operators, and perhaps, once the learning curve is passed by experienced operators, it may function as the intubation tool of choice for better laryngeal views in more difficult airways.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the proper approach to airway management in the delivery room.

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Index of Suspicion in the Nursery

1 Term Infant with Intractable Seizures and Bilateral Hydronephrosis

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AUTHOR DISCLOSURE Drs Bauer, Wraight, Rice, and Ikonomidou have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male neonate is born via vaginal delivery at 37 1/7 weeks' gestation to a healthy 30-year-old gravida 3, para 2 mother. The pregnancy had been complicated by polyhydramnios, severe fetal hydronephrosis, anti-Kell antibodies, and questionable fetal mega cisterna magna. Labor is induced secondary to worsening bilateral fetal hydronephrosis. The delivery is uncomplicated and Apgar scores are 9 and 9 at 1 and 5 minutes, respectively. Initial physical examination findings are significant only for left-sided club foot, and the infant is admitted to the well-newborn nursery. State newborn screening is performed 24 hours after birth, results of which are normal.

There is no significant familial history of congenital neurologic or urologic abnormalities, and both previous children of these parents are healthy. Amniocentesis performed during this pregnancy secondary to the bilateral fetal hydronephrosis had revealed a normal fetal microarray.

The infant is admitted to the NICU 3 days after birth secondary to hypernatremia (150 mEq/L [150 mmol/L]) and severe (grade 4) bilateral hydronephrosis confirmed with postnatal ultrasonography. While in the NICU, the neonate is noted to have episodes of lateral eye deviation, bilateral arm and leg twitching, and episodes of apnea. Electrolytes (excluding hypernatremia), glucose, and cranial ultrasonography findings are normal. A sepsis evaluation is completed and the infant is treated for 48 hours with ampicillin, cefotaxime, and acyclovir until blood, urine, and cerebrospinal fluid cultures return negative. Amplitude-integrated electroencephalography (EEG) findings are concerning for seizure activity and video EEG shows frequent multifocal epileptiform activity in both hemispheres indicative of abnormal cortical hyperexcitability, lowering the threshold for seizures. Following consultation with pediatric neurology he receives a loading dose of levetiracetam and maintenance therapy is initiated. Brain magnetic resonance imaging (MRI) reveals trace right occipital subarachnoid hemorrhage and trace infratentorial posterior fossa subdural hematoma thought to be secondary to birth trauma and not related to the seizure activity. Throughout the rest of the first week after birth, he has no further clinical seizure activity while receiving a maintenance dose of levetiracetam, and is able to take oral feeds of breast milk and formula.

In the meantime, further urologic evaluation is performed. Voiding cystourethrogram findings are normal, and mercaptoacetyltriglycine renogram with furosemide diuresis confirms bilateral ureteropelvic junction obstruction. Bilateral nephrostomy tubes are placed for renal decompression and plans are made for future bilateral ureteroplasty. Erythropoietin injections are started for preventing anemia in the setting of renal disease, and the neonate continues to receive prophylactic amoxicillin because of his severe bilateral hydronephrosis.

DISCUSSION

Progression

Following nephrostomy tube placement, the infant was again noted to have increasing frequency of apnea spells, and video EEG identified frequent seizure activity. Levetiracetam dosing was increased, and a loading dose of phenobarbital was administered, followed by maintenance with continued escalation of seizure frequency. Because of persistent and increasing seizure activity, further antiepileptic treatments were administered in an attempt to improve seizure control; these included vitamin B6, phenytoin, pyridoxal phosphate, leucovorin, topiramate, and carbamazepine, none of which reduced seizure frequency for any extended period. Most of the medications led to a transient favorable response for a few days, but the seizures eventually recurred.

The differential diagnosis for intractable seizures is vast and includes metabolic derangements (hypoglycemia, hyponatremia), infectious diseases (meningitis, sepsis), trauma (intraventricular hemorrhage, subarachnoid hemorrhage), and epileptic syndromes (channelopathies, multiple genetic syndromes). The differential is shorter with more rare associations if the urologic and musculoskeletal abnormalities are included, however this could easily be unrelated. A thorough infectious, neurologic, and genetic evaluation was undertaken. Multiple laboratory tests were performed including blood and urine for pipecolic acid, organic acids, acylglycines, lysosomal storage disease screen, α-aminoadipic semialdehyde, creatine biosynthesis panel, purines and pyrimidines, lactate, pyruvate, long-chain fatty acids, carnitine, acylcarnitine, biotinidase enzymes, and carbohydrate-deficient transferrins, all of which were unremarkable. Cerebrospinal fluid studies including neurotransmitters and amino acids were normal. Repeat brain MRI with magnetic resonance spectroscopy identified punctate loci of T1 and T2 hyperintensities in the right periatrial white matter of unknown clinical significance, but the findings were otherwise unremarkable. Ophthalmology evaluation was normal.

Diagnosis

After receiving the unremarkable infectious and metabolic laboratory results, a genetic epilepsy panel was sent to sequence 22 mutations known to cause infantile epilepsies; results showed abnormality for a heterozygous mutation in the *KCNT1* gene. This mutation, specifically coding DNA c.1420 C>T and amino acid p.Arg474Cys base changes, is associated with an autosomal dominant disorder, malignant migrating focal seizures of infancy (MMFSI), that is known to have a very poor prognosis. This neonate's clinical status continued to worsen, and he ultimately developed intractable seizures despite multiple antiepileptic therapies. The family decided to redirect the goals of care to focus on comfort and allow natural disease progression. The antiepileptic medicines were discontinued and he died 2 days later.

Condition

Neonatal seizures occur in 2.6 per 1,000 newborns and the frequency increases with prematurity and low birthweight. (1) Seizures in neonates may be clonic, tonic, myoclonic, or subtle and may present with lip smacking, abnormal eye movements, stereotypic movements such as bicycling, or central apnea. Most neonatal seizures are symptomatic and are caused by infections, metabolic derangements, structural central nervous system abnormalities, stroke, or hypoxic-ischemic encephalopathy. Genetic epilepsy syndromes become the focus of the diagnostic evaluation if infectious, structural, and metabolic evaluations have been unrevealing. Multiple genes have been associated with genetic epilepsy syndromes including *KCNQ2*, *KCNQ3*, *SCN1A*, *SCN9A*, *GABGR2*, and *KCNT1*. (2)

The *KCNT1* gene encodes a sodium-activated potassium (KNa) channel expressed throughout the nervous system, which regulates hyperpolarization after repetitive neuronal firing. (3) Multiple *KCNT1* gene mutations have been described and are considered causative for infantile epileptic encephalopathy syndromes. (2)(4) Two distinct seizure disorders, MMFSI and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), have been associated with gain-of-function mutations in *KCNT1*. (5) Patients with ADNFLE tend to have clusters of short motor seizures during sleep that are also associated with intellectual disability and psychiatric disorders, though seizures are not typically observed in infants. (6)

This patient's clinical course was most consistent with MMFSI, given the migrating focal seizures that were intractable to treatment. Previous cases have reported similar neurologic findings, including apnea caused by seizures and video EEG findings of asynchronous multifocal spikes through both cerebral hemispheres (Table). (3)(6) To our knowledge, this is the first reported case of a patient with MMFSI and a *KCNT1* mutation to present with urologic abnormalities.

Genetic testing in this patient confirmed the base change c.1420C>T inducing the amino acid change p.Arg474Cys, which is highly conserved among species in the *KCNT1*

TABLE. **Clinical Features of Patients with c.1420C>T *KCNT1* Mutations**

CLINICAL FEATURE	CURRENT PATIENT	PATIENT OF OHBA ET AL (6)	PATIENT OF SHIMADA ET AL (3)
Sex	M	M	M
Amino acid change	p.Arg474Cys	p.Arg474Cys	p.Arg474Cys
Age at seizure onset	3 days	0 days	9 days
Seizure type	Apnea eye deviations, tonic convulsions	Facial flushing eye deviations, tonic convulsions	Apnea, focal motor tonic convulsions
MRI findings	Right occipital SAH, infratentorial SDH (4 days of age)	Delayed myelination thin CC (6 months of age)	Delayed myelination thin CC (6 months of age)
EEG findings	Bilateral multifocal spikes, abnormal cortical, hyperexcitability	Bilateral multifocal spikes, suppression burst	Bilateral multifocal spikes
Non-neurologic findings	Club foot bilateral HN, UPJ obstruction	None described	None described
Intellectual disability	N/A	Yes	Yes

Arg=arginine; Cys=cysteine; CC=corpus callosum; EEG=electroencephalography; HN=hydronephrosis; MRI=magnetic resonance imaging; N/A=not applicable; SAH=subarachnoid hemorrhage; SDH=subdural hematoma; UPJ=ureteropelvic junction.

gene. Another neonate affected with the same *KCNT1* mutation had a brain MRI at 6 months of age, which demonstrated delayed myelination and a thin corpus callosum. (3) Another *KCNT1* mutation at p.Arg474 encoding histidine instead of cysteine secondary to DNA coding changes at c.1421G>A had similar clinical neurologic symptoms as seen in the current patient. (2) No previous patient with mutations in p.Arg474 had abnormal urologic findings.

Mutations found in the *KCNT1* gene induce learning impairment, psychiatric disorders, cardiac arrhythmias, sleep apnea, gastroesophageal reflux disease, microcephaly, spastic quadriparesis, and choreiform movements. (5)(6) EEG in patients with MMFSI shows epileptic spikes that migrate throughout multiple foci, often becoming more frequent as the patient ages, and tend to be resistant to antiepileptic pharmacotherapy. Treatment of these patients with multiple antiepileptic therapies (phenobarbital, carbamazepine, levetiracetam, lamotrigine, valproic acid, topiramate, clonazepam, clobazam, phenytoin, zonisamide, vigabatrin, intravenous immunoglobulin, adrenocorticotropic hormone, gabapentin, and the ketogenic diet) have been ineffective and all these children have significant developmental delay with frequent seizures. (6) Pharmacologic studies evaluating quinidine or ezogabine have shown some promise in decreasing seizure frequency for a period, but current studies have not shown significant improvement in developmental milestones. (7)(8)

The bilateral ureteropelvic junction obstruction leading to hydronephrosis in the current patient is an original finding in a patient with a confirmed *KCNT1* mutation. It is not clear if the *KCNT1* mutation is causative because there is no literature suggesting an association of this potassium channel and urothelial or renal cell development. Another potassium channel *KCNJ1* has been implicated in Bartter syndrome type 2, an electrolyte-losing nephropathy. However, this particular potassium channel does not appear to be present in the nervous system, nor is there a clear overlap with *KCNT1*. (9) This patient did not undergo whole exome sequencing to determine if other mutations were present that could have caused the abnormal urologic findings. As part of the evaluation in a patient with intractable seizures, renal ultrasonography should be considered to screen for urologic abnormalities potentially associated with genetic epilepsy syndromes.

Lessons for the Clinician

- When multiple congenital anomalies are known, it is important for the clinician to be aware of potential comorbidities in other organ systems.
- After the initial evaluation aimed at excluding infectious, metabolic, or structural abnormalities in intractable seizures, genetic epilepsy syndromes including channelopathies should be considered.

- Continued discussion with the family of a neonate with a genetic diagnosis that has a poor prognosis is important to determine the family's goals of care for their child.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Understand the differential diagnosis and evaluation of neonatal seizure.

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2 Is It Neonatal Purpura Fulminans?

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PRESENTATIONS

Case 1

A term newborn is first examined immediately after birth because of a widespread skin lesion that looks like cavernous hemangioma on his trunk and limbs (Fig 1). He had been born in a spontaneous vaginal delivery at the 40th week of gestation, with a birthweight of 3,450 g and an Apgar score of 9 and 10 at 1 and 5 minutes, respectively. The mother is a gravida 6, para 2, and abortus 3. Because she has had 3 spontaneous abortions, she undergoes a hypercoagulability profile whose findings are normal. The infant has a complete blood cell count that is normal, and shows no evidence of thrombocytopenia. The cutaneous lesions on his limbs, left palm, left knee, and right ankle are observed to be worsening at the age of 28 hours, and the skin looks like purpura with the beginning of necrosis (Fig 2). At this point, the blood tests show an elevation in the international normalized ratio (INR; 2.65) and a decrease in fibrinogen (110.7 mg/dL [3.25 μmol/L]), and he receives fresh frozen plasma (FFP). He is transferred to the hematology department in a tertiary hospital to monitor his clotting factors. The differential diagnosis includes sepsis, cutis marmorata telangiectasia congenital, and neonatal purpura fulminans. He is treated with heparin, FFP, and antibiotics. In spite of having received FFP for 24 hours, his protein C level is only 20% (normal values 80%–150%), and he is diagnosed as having protein C deficiency. Head computed tomographic angiography is performed to rule out vascular malformation and,

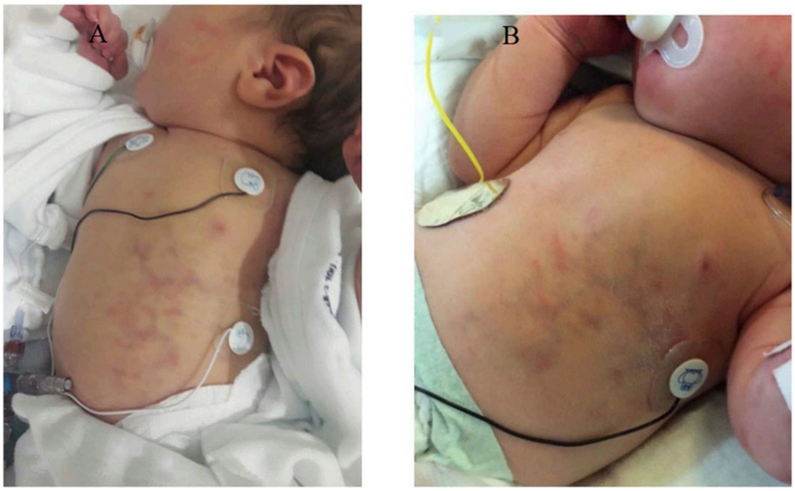

Figure 1. A and B. Case 1. Appearance of the chest immediately after birth.

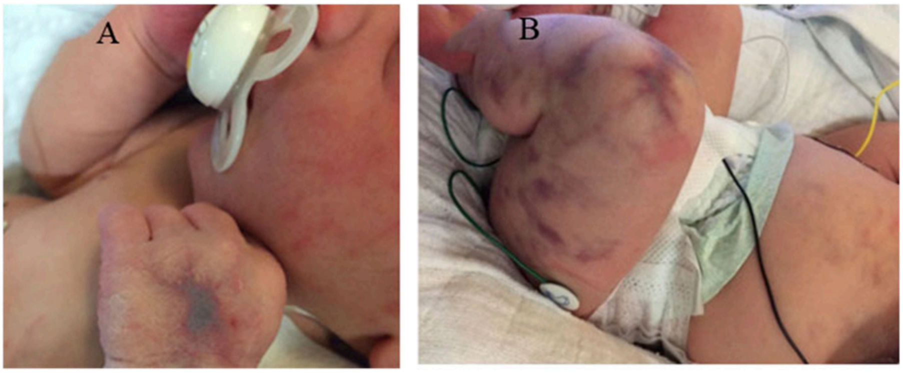

Figure 2. A and B. Case 1. Worsening of the lesions at 28 hours after birth.

although no malformation is found, a sinus vein thrombosis is suspected. No further changes in his condition are observed after 36 hours of additional monitoring in the PICU, and he is returned to the NICU with the recommendation to treat with low-molecular-weight (LMW) heparin twice daily and 1 unit of FFP once daily. The FFP is given as thrombolytic treatment for the skin areas with necrosis. On day 8 after receiving LMW heparin and FFP, protein C deficiency persists (30%), and the peak anti-Xa value is 0.48 (normal 0.3–0.8, therapeutic 0.5–1). The infant's condition remains stable, and on the 14th day of hospitalization, it is decided to stop the treatment with FFP though the protein C level is still low (36%). By the 18th day of hospitalization, the anti-Xa level is 0.66, and it is decided to discharge the infant and follow him at the hematology outpatient clinic. After 3.5 months of continuous LMW heparin treatment, he undergoes a head magnetic resonance imaging study, which rules out blood clots, malformations, and superficial vein thrombosis, whereupon the heparin treatment is stopped. Figure 3 demonstrates his condition at that time. Currently, the child is developing normally and the cutaneous manifestations are considerably faded.

Case 2

Five months after the first case, another newborn presents with similar manifestations of cutaneous discolorations. They had appeared on day 1 after birth as dark areas on the left knee. A management course of watchful waiting had been adopted, and at age 48 hours, the lesions are seen extending to the rest of the left leg (Fig 4) and to the back. At that point, a complete blood cell count, hypercoagulability profile, platelet count, and INR testing are conducted, results of which are all within normal range. The consulting hematologist advises prophylactic administration of 1 round of FFP and that the infant be transferred to a tertiary care PICU where he undergoes further observation and receives 1 injection of LMW heparin. When the clotting factors are negative for a hypercoagulability state, he is finally diagnosed as having cutis marmorata telangiectasia congenita. No further treatment is administered, and he is discharged from the hospital after a few more days of observation, with the parents instructed to follow up at the pediatric outpatient department in 2 months. His prognosis is expected to be very good.

DISCUSSION

Neonatal purpura fulminans (NPF) is a dermal microvascular thrombosis associated with disseminated intravascular coagulation (DIC) occurring in the newborn period. (1) It may manifest as acute DIC and hemorrhagic necrosis of the skin, and the affected areas may eventually become necrotic and gangrenous, resulting in loss of the extremities. (2)(3)

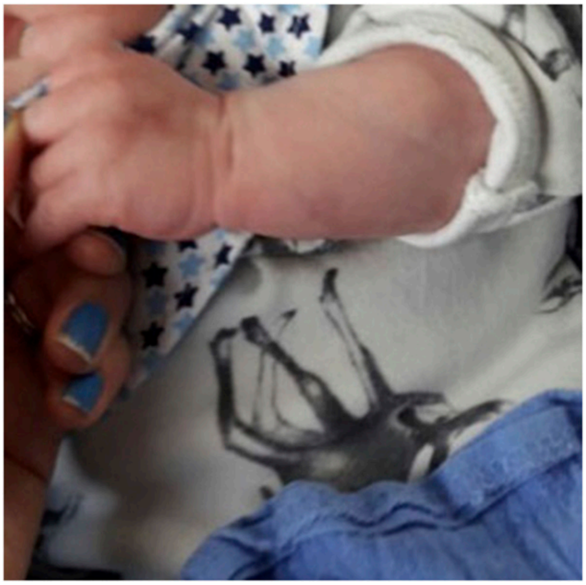

Figure 3. Case 1. After 3.5 months of continuous low-molecular-weight heparin treatment.

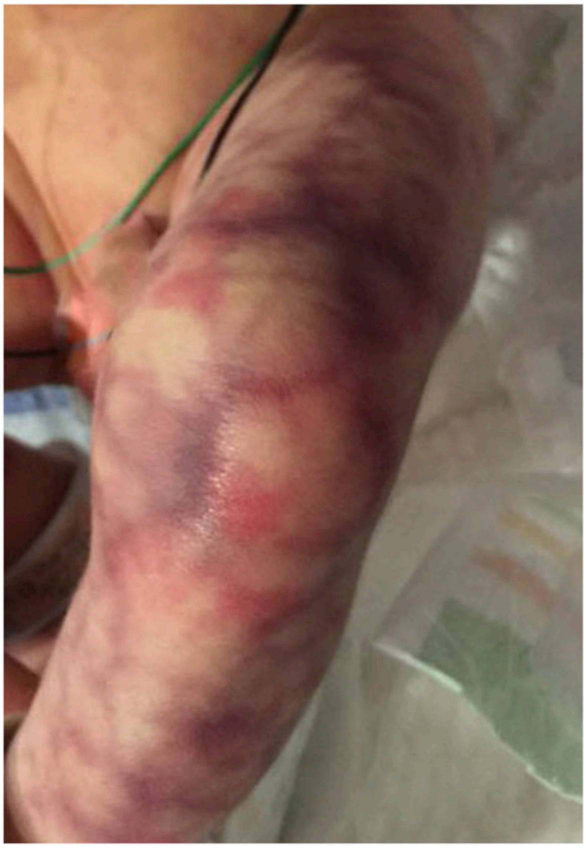

Figure 4. Case 2. After 48 hours of age, on admission to the NICU.

NPF is a rare condition caused by congenital or acquired deficiencies of protein C or S, and one that is often fatal if it is not treated early and effectively. The clinical severity of NPF may vary, depending on the underlying cause. The onset of symptoms is usually within 2 to 12 hours after birth. (2)(4) The skin lesions initially appear dark red and then become purple-black and indurated, occurring at previous sites of trauma, such as intravenous cannula insertion sites. Protein C deficiency is often associated with thrombosis of the cerebral vasculature. (5) In contrast, cutis marmorata telangiectasia congenita is a rare, mostly benign, localized or generalized, vascular anomaly of unknown etiology characterized by persistent cutis marmorata, telangiectasia, and phlebectasia. Diagnosis of cutis marmorata telangiectasia congenita is based on the clinical findings.

Lessons for the Clinician

- Dermal manifestations of an underlying disease/condition are unreliable for differential diagnosis.
- The detection of protein C deficiency confirmed a diagnosis of neonatal purpura fulminans in 1 newborn (requiring extended treatment), while the absence of abnormal laboratory results led to expectant management (no treatment) and uneventful course in another newborn diagnosed as having congenital cutis marmorata.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the cutaneous manifestations of neonatal hematologic disorders such as thrombocytopenia and coagulation disorders.

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Case 2: Is It Neonatal Purpura Fulminans?

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Index of Suspicion in the Nursery

3 Newborn with Asymmetric Crying Face

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AUTHOR DISCLOSURE Drs Amphaiphan, Tim-Aroon, and Ruangkit, have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 35-week-gestation male infant is delivered by cesarean section in the setting of maternal premature rupture of membrane and fetal nonreassuring heart tracing during the process of labor induction. The mother is a 30-year-old, gravida 2, para 1, healthy woman without significant medical history. Maternal antenatal testing results are normal with unremarkable prenatal complications. The neonate is the product of a nonconsanguineous marriage. At birth, the infant's head is delivered without instrumental assistance or birth trauma. He is vigorous and cries immediately after birth. Resuscitation efforts include a brief period of continuous positive airway pressure and oxygen support for increased work of breathing and desaturation; however, the infant recovers quickly and is transferred to the sick newborn unit in room air. His Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. Physical examination reveals a nondistressed premature infant with normal vital parameters. His birthweight, length, and occipitofrontal circumference are 1,840 g, 39 cm, and 31.5 cm, respectively. He is found to have an asymmetric crying face. When he is quiet or sleeping, his face appears symmetric. However, when he cries, the left corner of the mouth is drawn to the left and downward while the right corner does not move. The forehead wrinkling, nasolabial fold depth, and eye closure remain intact and equal on both sides (Fig 1). All extraocular muscle movements are intact. He has an overfolded helix with squared superior portion of helix of bilateral ears and micro-retrognathia (Fig 2). Other physical examination findings are unremarkable. There is no history of a similar condition on both sides of the family.

DISCUSSION

Diagnosis

On day 3 after birth, systolic ejection heart murmur grade 3/6 is heard mostly at the left upper parastenal border on routine daily physical examination. Chest radiography demonstrates normal lung parenchyma and globular-shaped heart with absence of a thymic shadow. Echocardiography reveals a 2.2-mm ostium secundum atrial septal defect with left-to-right shunt, 4-mm subpulmonic ventricular septal defect with left-to-right shunt, and double outlet of right ventricle. Cranial and renal ultrasonography findings are normal. Chromosome study reveals 46,XY. Fluorescent in situ hybridization for 22q11 shows deletion. The neonate is diagnosed with congenital hypoplasia of depressor angularis oris muscle (CHDAOM) on the right side and 22q11.2 deletion syndrome. Further laboratory investigation

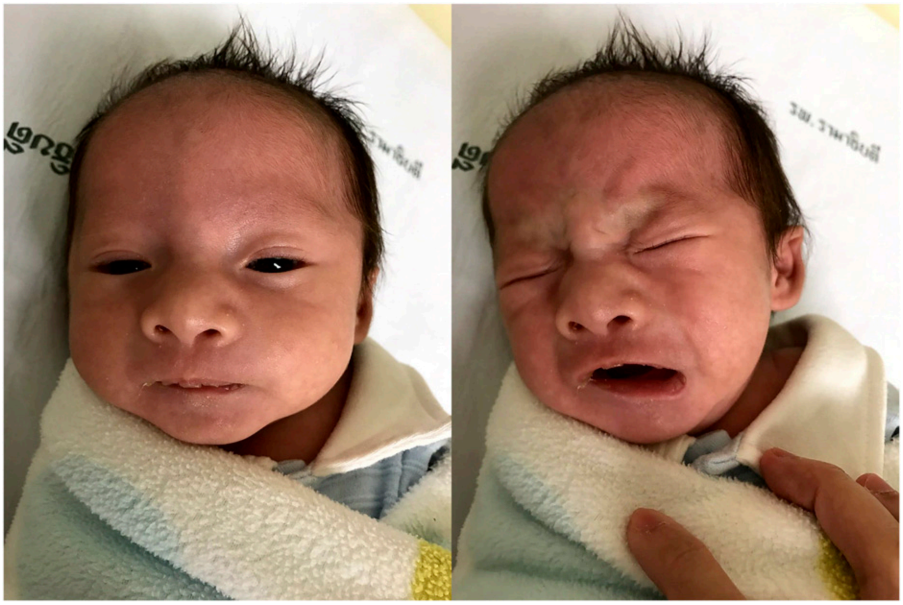

Figure 1. When the infant is at rest, the face appears symmetrical (left). When the infant is crying, the left corner of the mouth is drawn to the left and downward (right).

during hospitalization reveals a normal complete blood cell count, electrolytes, calcium, phosphate, and parathyroid hormone levels.

Condition

Asymmetric crying facies (ACF) is a condition in which an infant's face appears symmetric at rest and asymmetric when crying, that is, 1 corner of the mouth is pulled downward while another corner is not moving. (1) ACF can result from facial nerve compression to mandibular branch of facial nerve during the process of labor, leading to nerve injury. Another cause of ACF is hypoplasia or agenesis of the muscles that involve downward movement of lips, namely, depressor angularis oris muscle and depressor labii inferioris muscle, the latter being less common. ACF is a minor anomaly occurring in 3 to 8 per 1,000 live births and predominantly affects the left side more than the right side. (2) This condition needs to be differentiated from facial nerve paralysis, which can be congenital (due to genetic defects) or, more commonly, acquired (from obstetric-related nerve trauma). In ACF, facial asymmetry presents as 1-sided downward movement of the mouth and symmetric eye closure, whereas in true facial nerve paralysis, all the facial muscles on 1 side are affected.

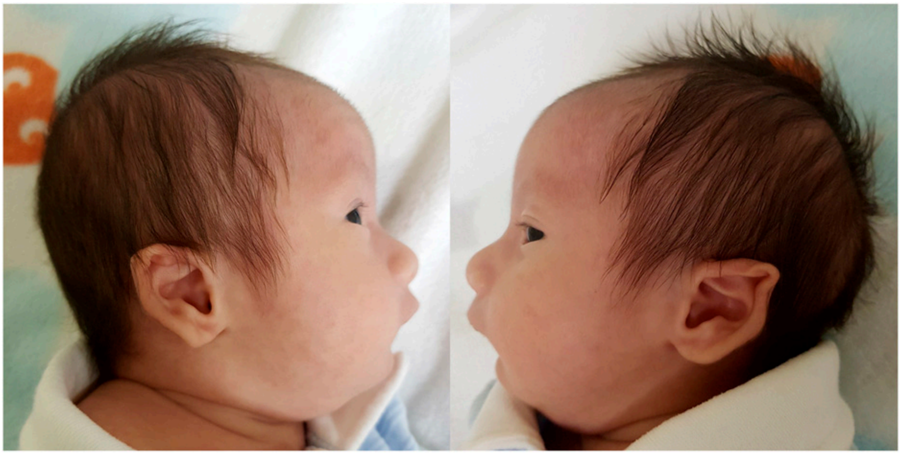

Figure 2. Infant facial features from right and left lateral views, showing overfolded helix with squared superior portion of helix of bilateral ears and microretrognathia.

The ACF that results from CHDAOM can be differentiated from the ACF caused by trauma using several approaches. First, based on the patient history, if obstetric risk factors for fetal compression are present (eg, large fetus, difficult labor, instrumental delivery), nerve compression can be suspected. Second, mandibular asymmetry and maxillary-mandibular asynclitism (nonparallelism of the gums) found during physical examination are important clues to the diagnosis of ACF resulting from nerve branch injury. Finally, further investigation using ultrasonography of facial muscles to ensure the absence or hypoplasia of depressor angularis oris muscle and electrodiagnostic testing to ensure paucity of motor unit potentials, lack of muscle fibrillation, and normal conduction velocity of the facial nerves may be useful to confirm a diagnosis of CHDAOM. (3)

The cause of the CHDAOM is not known; however, the pattern of inheritance does not suggest a single gene disorder, but favors complex multiple causative factors. (4)(5) Many other congenital anomalies may be present in infants with ACF that results from developmental error in muscle or nerve development. (6) The risk of associated anomalies in infants with ACF is 3.5-fold higher than in normal infants and it is reported that 5% to 70% of infants with ACF have associated anomalies, depending on the population and study criteria. (2) The common associated anomalies occur in the head and neck (48%), cardiovascular system (44%), musculoskeletal (22%), genitourinary tract (24%), central nervous system (10%), gastrointestinal tract (6%), and miscellaneous minor anomalies (8%). (4) Common head and neck anomalies are auricular malformation (dysplastic or hypoplastic ears, low-set ears, preauricular tags), mandibular or maxillary hypoplasia and palate anomaly. Common cardiac anomalies are atrial septal defect, ventricular septal defect, and patent ductus arteriosus. Other types of congenital heart diseases have also been reported. In other organ systems, various associated anomalies include those of the musculoskeletal system (syndactyly, clinodactyly, cortical thumb, hemivertebra), genitourinary system (inguinal hernia, renal hypoplasia, vesicoureteral reflux, cryptorchidism), central nervous system (auditory dysfunction, agenesis of the corpus callosum, hydrocephalus, brain cyst), and gastrointestinal system (esophageal atresia, imperforate anus, megacolon). (2)(4)(7)

The association of ACF and 22q11 deletion syndrome is well-described. Pasick et al report a 14% incidence of ACF in patients with a 22q11 deletion syndrome, which is significantly higher than in the general population. (6) In addition, various genetic syndromes, including trisomy 21, 4p deletion, Klinefelter syndrome, and VATER association (vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia), are diagnosed in patients with ACF. (2)(5)(7)

Treatment

In the case of nerve compression, the prognosis is good and spontaneous resolution is expected. In contrast, in the case of CHDAOM, spontaneous resolution is less likely. (2) However, treatment of CHDAOM is usually not required because the asymmetry will become less obvious as other facial muscles compensate for the child's facial expression when the child grows up. In those who need treatment for cosmetic purposes or to correct functional deficit and improve quality of life, various therapeutic strategies are available. These include plastic-reconstructive procedures on the lower lip on the affected side or additional blocking/weakening of the contralateral nonaffected side. (8) Associated congenital malformation and genetic syndromes are managed accordingly.

Progression

The infant described here developed clinical congestive heart failure at 1 week of age. Treatment consisted of fluid restriction, diuretics (furosemide and spironolactone), and digitalis glycosides (digoxin), and resulted in significant clinical improvement. The patient passed the otoacoustic emissions hearing screening and was discharged from the hospital in stable condition at the age of 2 weeks. The parents were counseled about the prognosis of CHDAOM and 22q11.2 deletion syndrome. Parental genetic tests to detect chromosome 22q11 deletion were recommended to provide guidance for future pregnancies.

Lessons for the Clinician

- Asymmetric crying facies (ACF) is not uncommon and can be found in approximately 3 to 8 per 1,000 live births.
- Physicians should be able to differentiate between ACF and true facial nerve paralysis.
- Congenital hypoplasia of depressor angularis oris muscle can be associated with other congenital malformations and genetic syndrome. Therefore, a thorough physical examination and diagnostic evaluation are required.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the significance of persistent neuromotor abnormalities in infancy (including asymmetries).
- Know the clinical and diagnostic features of the DiGeorge sequence (velocardiofacial syndrome, 22q11 deletion).

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Parent Resources from the AAP at HealthyChildren.org

- Micrognathia & Pierre Robin Sequence: https://www.healthychildren.org/English/health-issues/conditions/Cleft-Craniofacial/Pages/Micrognathia-Pierre-Robin-Sequence.aspx
- Infantile Spasms: What Parents Need to Know: https://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Infantile-Spasms-What-Parents-Need-to-Know.aspx
- Children with Facial Asymmetry: https://www.healthychildren.org/English/health-issues/conditions/Cleft-Craniofacial/Pages/Children-with-Facial-Asymmetry.aspx
- Umbilical Cord Care: https://www.healthychildren.org/English/ages-stages/baby/bathing-skin-care/Pages/Umbilical-Cord-Care.aspx

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at http://patiented.aap.org.

Case 3: Newborn with Asymmetric Crying Face

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Red and Swollen Umbilical Region

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THE CASE

At 18 days of age, a male infant born at term presents with redness and swelling surrounding the umbilicus (Fig 1).

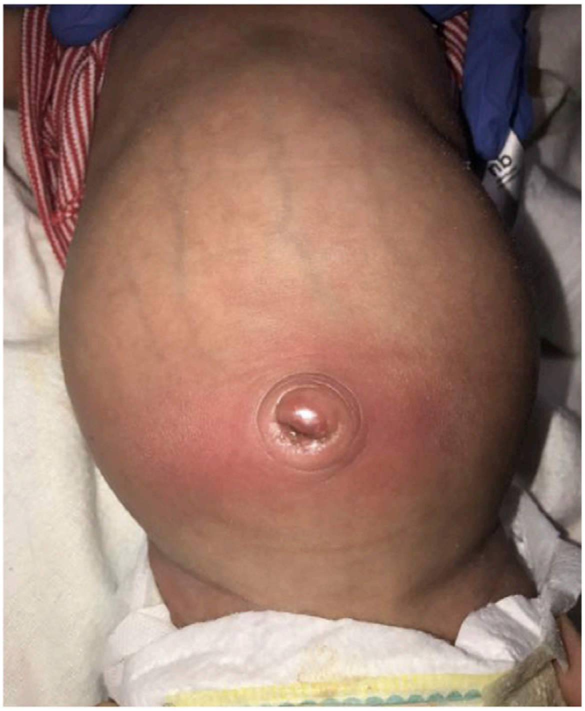

Figure 1. Abdomen at admission.

PRENATAL AND BIRTH HISTORIES

- Born to a 22-year-old, gravida 2, para 2 woman in good health
- Benign prenatal maternal screens including rubella immune, rapid plasma reagin negative, human immunodeficiency virus negative, group B *Streptococcus* negative
- Benign prenatal course with normal fetal survey
- 8 days before delivery fetal ultrasonography revealed an amniotic fluid index of 1.5 with possible rupture of membranes
- Infant born via cesarean delivery because of nonreassuring fetal heart tones in the setting of persistent oligohydramnios; there were no signs of chorioamnionitis
- Estimated gestational age: 39 weeks and 2 days
- Birthweight: 3.04 kg (26th percentile)
- Apgar score: 9 at 1 minute of age, 9 at 5 minutes of age
- Infant was discharged from the hospital on the 4th postnatal day

AUTHOR DISCLOSURE Drs Kumar, Niemi, Thorson, and Palma have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

At 13 days of age, the infant had spontaneous separation of the umbilical stump following routine dry umbilical cord care. At 17 days of age, the infant's mother noted redness around the umbilicus, which progressed rapidly throughout the day. His mother also noted scant yellow drainage from the umbilicus. She brought him to the emergency department at 18 days of age. At that time, he was afebrile, breastfeeding well, and acting appropriately, with normal voiding and stooling patterns.

Vital Signs

- Heart rate: 168 beats/min
- Respiratory rate: 30 breaths/min
- Temperature: 97.9°F (36.6°C)
- Oxygen saturation: 97% in room air

Physical Examination

- Head: Normocephalic; normal, open, flat fontanelles; symmetric facies; patent nares
- Oral cavity: Pink mucosae; intact palate; scattered, white 2- to 3-mm papules on anterior surface of gingiva
- Abdomen: Approximately 7×7–cm tender area of erythema and swelling around the umbilicus with scant yellow drainage from the umbilicus; positive bowel sounds; mildly distended but soft abdomen
- Cardiovascular: Normoactive precordium; regular rate and rhythm; no murmur, rub, or gallop
- Genitourinary: Normal male genitalia, testes descended bilaterally
- Skeletal: Spine normal appearing
- Skin: No icterus or rash, slate gray patch above gluteal cleft; vernix smeared in skin creases of legs
- Neurologic: Normal strength, tone, suck reflex, and palmar/plantar grasp age appropriate

Laboratory Studies

- White blood cell count: 15,100/μL (15.1×10^9/L) with 56% neutrophils, 30% lymphocytes
- Platelet count: 553×10^3/μL (553×10^9/L)
- Chemistry
  - Sodium: 134 mEq/L (134 mmol/L)
  - Potassium: 5.8 mEq/L (5.8 mmol/L)
  - Chloride: 97 mEq/L (97 mmol/L)
  - Bicarbonate: 23 mEq/L (23 mmol/L)
  - Glucose: 116 mg/dL (6.4 mmol/L)
  - Blood urea nitrogen: 4 mg/dL (7.8 mmol/L)
  - Creatinine: 0.21 mg/dL (18.5 μmol/L)
- Transaminases
  - Alanine aminotransferase: 6 U/L
  - Aspartate aminotransferase: 31 U/L
- Alkaline phosphatase: 289 U/L
- Total bilirubin: 1.25 mg/dL (21 μmol/L)
- C-reactive protein: 7.7 mg/dL (reference range, < 0.9 mg/dL)

A neonatologist was consulted and further testing was performed.

PROGRESSION

In the emergency department, the infant was noted to have tachycardia, prompting the team to administer a normal saline bolus. The team then consulted with the neonatologist. Although the infant appeared well, the neonatologist recommended further evaluation and management. Cultures were performed on peripheral blood samples and drainage from the umbilical cord. The infant was given intravenous vancomycin and gentamicin before being transferred to the NICU in stable condition. The infant then underwent complete abdominal ultrasonography (Fig 2).

DIFFERENTIAL DIAGNOSIS

For this term infant with redness and swelling of umbilical cord, the differential diagnosis included:

- Allergic reaction
- Cellulitis
- Neutrophil function defects (if delayed umbilical cord separation)
- Omphalitis
- Omphalomesenteric duct remnant (patent omphalomesenteric duct, sinus tract)
- Umbilical granuloma
- Urachal remnant (patent urachus, urachal sinus, infected urachal cyst)

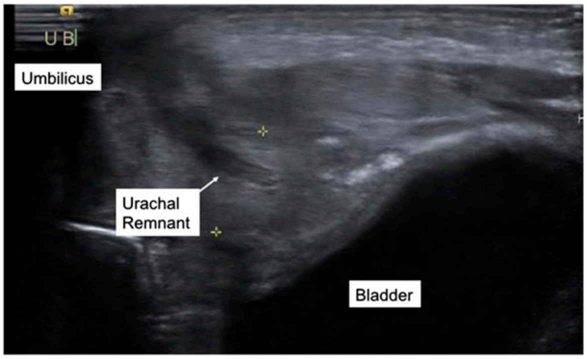

Figure 2. Ultrasonographic scan of abdomen reveals tract from bladder to umbilicus (ie, urachal remnant).

ACTUAL DIAGNOSIS

Omphalitis with urachal remnant

MANAGEMENT

Ultrasonography of this infant's abdomen showed soft tissue swelling consistent with omphalitis as well as a thickened communicating tract from the bladder to the umbilicus. Culture of the umbilical cord drainage grew methicillin-sensitive *Staphylococcus aureus* (blood cultures remained negative) and antibiotics were narrowed to intravenous cefazolin after broad antibiotic treatment for 3 days. The infant's C-reactive protein decreased with time. He continued to remain well appearing, afebrile, and tolerated oral feedings. By the 10th day of antibiotic treatment, the redness and swelling surrounding his umbilicus had resolved (Fig 3).

WHAT THE EXPERTS SAY

Omphalitis is an infection and inflammation of the umbilical cord stump that is characterized by erythema, swelling, and tenderness of the periumbilical region, with severity ranging from isolated discharge from the umbilical cord to subcutaneous and peritoneal inflammation. (1)(2) Although improvements in cord care techniques have made this condition rare in hospitalized newborns in developed countries, the incidence is much greater worldwide, approaching 20% in some developing countries. (3) Risk factors for omphalitis include poor umbilical cord care, protracted labor, and prolonged rupture of membranes, as well as anatomic abnormalities involving umbilical remnants (eg, patent urachus). (1) Causative organisms include *S aureus* and *Streptococcus* species, as well as gram-negative rods including *Escherichia coli*. (4) Infections can spread locally to the skin and abdominal wall, or can track through the umbilical and portal vessels to the liver and bladder. Complications of such infections can be life threatening. Necrotizing fasciitis is a rare complication that results from pathogens tracking along fascial planes, which can rapidly lead to tissue necrosis and sepsis. Infection of the urachal remnant that connects the umbilicus to the bladder can create an abscess that requires drainage. An infection of portal vessels can result in thrombosis with subsequent liver failure. (4)

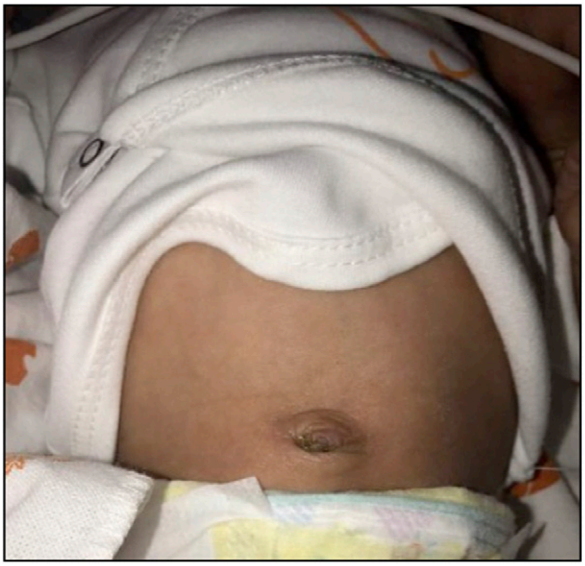

Figure 3. Abdomen after antibiotic treatment for 10 days.

Evaluation of an infant with erythema and swelling of the umbilicus requires a thorough physical examination and immediate imaging studies. Rare inherited neutrophil function deficiencies such as leukocyte adhesion defects should be considered if cord separation is delayed with concomitant neutrophilia. (5) The umbilical cord of the infant described in this case separated at 13 days (slightly late but within the normal timeframe). After establishing omphalitis as a likely diagnosis, evaluation for potential complications involving the liver, bladder, and peritoneum is important. Early ultrasonography of the abdomen in this patient helped to rule out an intra-abdominal abscess and necrotizing fasciitis that would have required surgical drainage.

Abdominal ultrasonography also identified an abnormal connection between the umbilicus and bladder in this patient. Abnormalities can derive from the urachus, an embryologic structure between the umbilicus and bladder that is typically obliterated before birth and results in 1 of the following 4 anomalies: patent urachus, urachal cyst, urachal sinus, and urachal diverticulum. A patent urachus may present with urine draining from the umbilicus. Incomplete obliteration of the urachus would result in an isolated urachal cyst containing epithelial cells or urachal sinus that communicates with the umbilicus, which could serve as a nidus of infection. (6) Although a urachal remnant was identified in this patient, its type could not be determined, nor could it be confirmed whether it was responsible for the infection in this patient. A skin infection is likely, given the type of organism isolated and the signs of inadequate hygiene with persistent vernix noted in the infant's skin creases. The source of infection did not influence the immediate treatment, because broad-spectrum antibiotics would be indicated initially, regardless of the anatomic abnormality. This patient will require follow-up abdominal ultrasonography after treatment to clarify the diagnosis and ensure no anatomic abnormalities predisposing to infection remain. It is likely that the inflammatory process, healing, and subsequent scar formation will close off this tract, obviating the need for further intervention. (7)

Omphalitis is a potentially fatal infection of newborns; timely diagnosis, evaluation for complications, and administration of antimicrobial therapy can be lifesaving.

Acknowledgments

We thank J.L. Aby and J. Santoro for helpful discussions.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical and laboratory features, treatment, and complications of neonatal omphalitis.
- Know how to evaluate and manage disorders of the umbilical cord, including granulomas, persistent omphalomesenteric duct remnant, and patent urachus.

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ANSWER KEY FOR MAY 2018 NEOREVIEWS

Corneal Opacities in the Neonate: 1. C; 2. A; 3. D; 4. E; 5. C.

Mandibular Distraction for Micrognathia: 1. B; 2. D; 3. A; 4. C; 5. C.

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Answer Key appears on page e360.

Birth Cohort Studies and the Early Origins of Adult Health and Disease

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Education Gap

Preconception, prenatal, and birth cohort studies are time, effort, and money consuming, and are less common than other epidemiologic study designs. Clinicians need to be aware of the main characteristics and availability of preconception, prenatal, and birth cohort studies to prioritize evidence from this type of research when studying early-life origins of adult disease.

Abstract

Prenatal and birth cohort studies, including those that start before conception, are an epidemiologic study design that best allows for the investigation of early-life origins of adult disease. This article reviews the definition and methodology of a cohort study. We also identify the worldwide locations of the most important preconception, prenatal, and birth cohorts that have been studied, as well as describe their characteristics. Finally, we examine the importance of these studies in the context of life-course epidemiology research and discuss why new studies of this type are needed. Preconception, prenatal, and birth cohorts provide insights into the mechanism of risk and protection across the life course and between generations, and have contributed significantly to what is known today regarding the developmental origins of health and disease hypothesis.

Objectives After completing this article, readers should be able to:

1. Define a cohort study and describe its main methodologic characteristics.
2. Identify the most important preconception, prenatal, and birth cohort studies worldwide and their chief characteristics.
3. Recognize the relevance of cohort studies for the study of early-life origins of adult health and disease.
4. Describe why new preconception, prenatal, and birth cohort studies are needed in different settings (ie, low-, middle-, and high-income countries).

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ABBREVIATIONS

ALSPAC	Avon Longitudinal Study of Parents and Children
IJE	International Journal of Epidemiology

WHAT IS A COHORT STUDY?

A cohort study is a type of observational epidemiologic study in which the status of individuals regarding the exposure of interest determines their selection for the study. Members of the cohort are then tracked from the time of exposure until the occurrence of the outcome(s) of interest. The presence or absence of exposure to a particular event/variable results in the formation of 2 groups: exposed and unexposed. At the end of the follow-up period, the exposed and unexposed groups are compared in terms of the frequency of illness/injury and other outcomes of interest. (1)

Depending on the reference time point for the exposure of interest and the time at which the study starts, cohort studies can be classified as prospective, retrospective, or ambispective (Fig 1). In a prospective cohort study, exposure data are collected at study entry (in the present), and cohort members are then followed until the outcome is achieved (in the future). In a retrospective cohort study, exposure and outcome are defined on the basis of data collected before the study outset (in the past). A cohort study can present characteristics of both designs, in which case it is considered an ambispective study. In an ambispective cohort study design, exposure is defined at a time in the past, the outcome is identified in the present, and cohort members can be followed to identify the incidence of new cases. (2)

Cohort membership can be classified as fixed or dynamic, depending on the period during which the subjects are enrolled. Fixed cohorts are those in which the subjects are enrolled at the beginning of the study (recruitment period) and no new subjects are enrolled during the follow-up period. Dynamic cohorts allow the entry and exit of subjects during the follow-up period. (3)

To create a cohort, the sample can be selected from the general population or from special exposure groups, depending on the purpose of the study and the exposure of interest. Cohorts selected from the general population allow quantification of exposure and outcome variables, and examine their relationship at the population level. However, for rare or unusual exposures, the selection of special exposure groups is more likely to provide adequate number of subjects and individual exposure data compared with a cohort selected from the general population. First, an exposed cohort (eg, a group of individuals exposed to a specific environmental contaminant) and a sample of unexposed individuals are identified. Subsequently, the 2 groups are followed longitudinally to assess the incidence of the outcome of interest. (1)(2)(3)

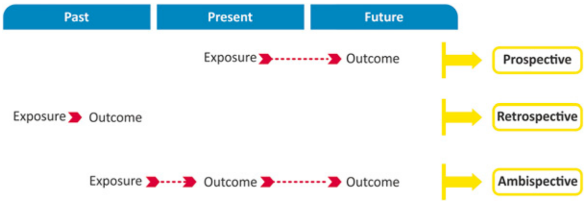

Figure 1. Representation of the reference time points for exposure data and outcomes of interest in cohort studies.

The necessary prerequisite of a cohort study is the guarantee of a temporal relationship, given that the exposure necessarily precedes the occurrence of the outcome. Risk can be assessed directly by calculating incidence measures. (4) Frequent follow-up evaluations of the cohort over time allow the formulation of new hypotheses and the investigation of multiple outcomes throughout life. (1)

One of the main disadvantages of a prospective cohort study is the virtually inevitable loss of members during follow-up (attrition bias). If the losses to follow-up differ between the exposed and unexposed groups, the risk can be under- or overestimated, depending on whether the losses are attributable to the outcome measure. (4) The high cost of long follow-up periods is another major disadvantage of cohort studies. Cohort studies often require relatively large samples to obtain scientifically relevant evidence, especially for outcomes with a low prevalence in the population. (5) The primary disadvantage of retrospective cohort studies is the investigator's inability to control data collection. As a result, the data may be incomplete, imprecise, or inconsistently measured between subjects; retrospective cohort studies are also susceptible to recall or information bias.

BASIC STAGES OF A COHORT STUDY

The execution of a cohort study involves the meticulous planning of all its stages: the definition of the study objectives; selection of the study population and the exposures and outcomes that will be investigated; creation of instruments for data collection and measurement; development of strategies to avoid losses to follow-up; execution of a pilot study before beginning definitive data collection, and the data analysis plan after completion of the follow-up (Fig 2). (6)

It is necessary to define the population in which the effects of a given exposure on a given outcome will be investigated. Depending on the purpose of the study and the hypotheses to be tested, the sample can be selected from the general population or from specific exposure groups. After the cohort with the relevant exposure groups has been defined and recruited, the cohort members are followed over time for assessment of outcomes of interest. The exposure and outcome variables should be measurable and clearly defined. In prospective cohorts, losses to

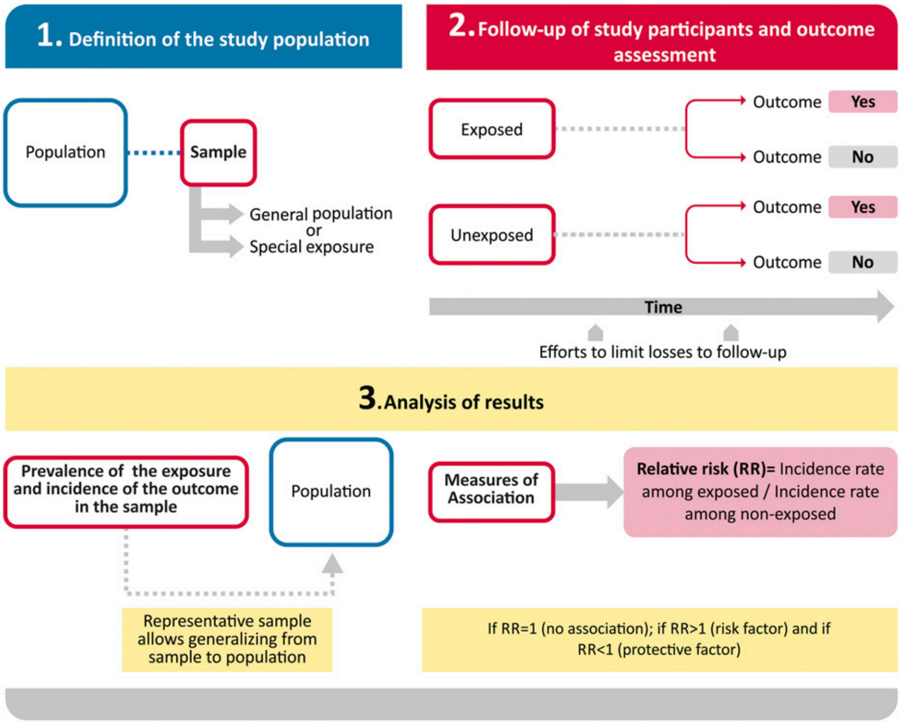
1. Definition of the study population
Population
Sample
General population
or
Special exposure
2. Follow-up of study participants and outcome assessment
Exposed
Unexposed
Outcome Yes
Outcome No
Outcome Yes
Outcome No
Time
Efforts to limit losses to follow-up
3. Analysis of results
Prevalence of the exposure and incidence of the outcome in the sample
Population
Representative sample allows generalizing from sample to population
Measures of Association
Relative risk (RR)= Incidence rate among exposed / Incidence rate among non-exposed
If RR=1 (no association); if RR>1 (risk factor) and if RR<1 (protective factor)

Figure 2. Basic procedures of a cohort study.

follow-up should be minimized so that risk measures can be estimated without bias. Subsequently, the incidence of the outcome among exposed and unexposed groups is compared through an association measure such as relative risk. (1)

PRECONCEPTION, PRENATAL, AND BIRTH COHORT STUDIES

The types of cohort studies that best allow the study of early predictors of disease risk are preconception, prenatal, and birth cohorts. Birth cohorts are composed of individuals whose common event is birth at a given place and time. In these studies, data related to prenatal exposures are collected retrospectively. Cohort studies that begin in pregnancy and those that begin in the preconception period are particularly interesting because they identify fetal and preconception exposures in real time. However, the gathering of information related to pregnant women requires greater logistical planning and incurs higher costs than maternal/newborn data assessed at birth. (2)(7)

Birth and prenatal cohorts have contributed much of what is known today about the early-life origins of adult disease, and are the main source of data for life course epidemiology. The life course epidemiology framework encompasses the biological, behavioral, and psychosocial processes that occur throughout the life of individuals, linking adult health and the risk of becoming ill with physical or social exposures that occurred earlier in life (during gestation, infancy, childhood, adolescence, or the early stages of adulthood) or in previous generations. (8)

LOCATION OF THE MAIN PRECONCEPTION, PRENATAL, AND BIRTH COHORTS WORLDWIDE

The *International Journal of Epidemiology* (IJE) features a Cohort Profile section, in which it publishes the methodology of cohort studies conducted around the world. The studies published in that section are those for which the baseline data collection has been completed, basic descriptive data have been provided, and follow-up plans for cohort members have been clearly outlined. Preference is given to studies involving cohorts of more than 1,000 members and for whom study-specific follow-up data were collected. In that same section, the IJE also publishes profiles of cohort consortia as long as they present aggregate data. (9)

With the objective of identifying preconception, prenatal, and birth cohort studies with published methodology, we performed a bibliographic search of the PubMed database. The search strategy included title and journal searches with the terms “cohort profile” and “*International Journal of Epidemiology*,” respectively. Cohorts and cohort consortia in which the members were enrolled during childhood or thereafter were excluded. We screened the articles by reading the titles and the full text. The cohort data, which were extracted and imported into a spreadsheet, included the following:

- Cohort name
- Year of publication of the study
- First year of member recruitment
- City and country
- Stage of life during which members were recruited (preconception, prenatal, or at birth)
- Birth data collection (prospective or retrospective)
- Type of membership (fixed or dynamic)
- Sample selection (from the general population or from specific exposure groups)
- The initial number of members
- The age of the members at the most recent follow-up evaluation.

We considered all articles published until November 14, 2017.

Figure 3 shows a flow chart of the study selection process. After the removal of duplicates, we identified 352 studies published in the IJE Cohort Profile section. Of those, 84 were preconception, prenatal, or birth cohorts and 4 were birth cohort consortia.

Of the 84 cohorts identified, 41 were birth cohorts, 41 were prenatal cohorts, and 2 were preconception cohorts. A prospective design was used in 64 studies, 38 were population-based, and 72 studies involved cohorts with fixed membership. We identified 19 multicenter cohort studies, 14 of which were single-country studies and 5 of which were conducted in 2 or more countries. The cohorts comprised members who were born before the 1950s (n=13 studies), between 1950 and 1989 (n=19 studies), and in the 1990s (n=52 studies). More than a third of the identified cohort studies published their methodology between 2015 and November 2017 (Table 1).

Of the 84 cohorts identified, 40 were located in Europe, 4 in Africa, 13 in the Americas, 15 in Asia, and 12 in Oceania (Table 2). Most of the European cohorts were in England. In the Americas, most of the cohorts were in the United States or Brazil. In Asia, most of the cohorts were in East Asia (China or Japan) and South Asia (India). In Oceania, most of the cohorts were in Australia. According to the World Bank classification of countries by income group, (10) 63 of the cohorts belonged to high-income countries, 15 to upper middle-income countries, and 6 to lower middle-income countries. The number of individuals enrolled at the beginning of the studies was significantly higher in the cohorts in high-income countries compared with those from low- and middle-income countries (Table 3). Figure 4 shows the location of the 84 cohorts on a world map.

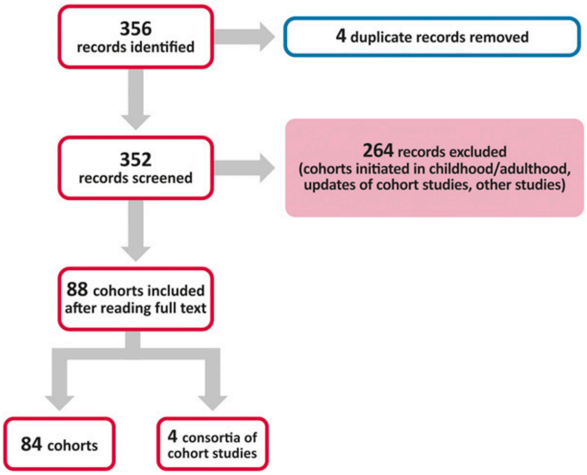
356 records identified
4 duplicate records removed
352 records screened
264 records excluded (cohorts initiated in childhood/adulthood, updates of cohort studies, other studies)
88 cohorts included after reading full text
84 cohorts
4 consortia of cohort studies

Figure 3. Flow chart for the search and selection stages of the preconception, prenatal, and birth cohort studies.

The characteristics of the cohorts varied according to the income level of the country in which they were located. One of the characteristics of high-income countries is the development of cohorts with birth registration data and national databases. In these countries, data related to births occurring decades ago are available in historical records, usually tracked by a personal record number. The availability of such data creates the opportunity for monitoring large populations and participants at advanced ages. For example, the retrospective Nordic Perinatal Bereavement Cohort study, which was conducted in Denmark, Finland, and Sweden, used decades of follow-up data obtained from population records and involved more than 7 million individuals born between 1973 and 2007. (11) In addition, the Hertfordshire cohort studies, conducted in England, included 3,225 individuals born between 1931 and 1939, (12) as well as 3,477 individuals born between 1920 and 1930. (13) Other characteristics that differentiate cohort studies conducted in high-income countries from those conducted in other countries include the greater number of follow-up evaluations performed, longer follow-up periods, and greater sophistication of relevant measurements. (14)(15)(16)(17) Another interesting aspect of such cohort studies is that the life course epidemiology approach is not limited to individuals of a single generation; the descendants of cohort members are often being monitored as well, which allows analyses across generations. For example, monitoring of the second generation of participants has already begun for the United Kingdom–wide 1946 and 1970 cohorts, (14)(16) as well as for the Avon Longitudinal Study of Parents and Children (ALSPAC). (17)

Although prenatal and birth cohorts in upper middle-income countries are less common than are those in high-income

TABLE 1. **Main Characteristics of the Preconception, Prenatal, and Birth Cohorts Identified**

VARIABLE	NO.	%
Initiation of the cohort		
Birth	41	48.8
Prenatal	41	48.8
Preconception	2	2.4
Study design		
Prospective	64	76.2
Retrospective	20	23.8
Cohort membership		
Fixed	72	85.7
Dynamic	12	14.3
Base		
Sample of the target population	46	54.8
All of the target population	38	45.2
Multicenter		
No.	65	77.4
In a single country	14	16.7
In ≥2 countries	5	5.9
Birth year		
Pre-1950	13	15.5
1950–1989	19	22.6
1990 or after	52	61.9
Year of publication		
2005–2009	21	25.0
2010–2014	28	33.3
2015–2017[a]	35	41.7
Total	84	100.0

[a] *Through November 2017.*

countries, some of the former are noteworthy. This is especially true of the cohorts in the city of Pelotas, Brazil, located in the southern region of the country. The first Pelotas birth cohort was initiated in 1982 and involved 5,914 children. (18) Subsequent cohorts were initiated in 1993, 2004, and 2015. With 3 decades of work, more than 24,000 individuals studied throughout their life, hundreds of follow-up evaluations performed, and thousands of variables collected, the Pelotas birth cohort studies are the largest population-based birth cohort studies in developing countries and have the lowest rates of loss to follow-up of such studies. (18)(19)(20)(21) Some cohort studies conducted in other upper middle-income countries, including South Africa, (22) Jamaica, (23) and the Philippines, (24) have cited problems with family migration, early childhood deaths, and a lack of financial resources as reasons for losses to follow-up.

In cohort studies conducted in lower middle-income countries, the collection of data related to individuals at birth is hampered by cultural practices of delivery outside the hospital setting and incomplete or absent birth records. (25)(26)(27) In such countries, cohort studies also encounter problems with losses to follow-up, mainly due to high infant mortality and internal migration. (25)(26)(27)(28)

Of the 84 cohort studies identified, only 2 involved preconception cohorts. In the 2007 Snart-Gravid cohort from Denmark, 2,288 women of reproductive age were evaluated before and after conception and were monitored until delivery. (29) The 2009 “LIFE” cohort study conducted in India collected data on 980 women before gestation and their offspring up to 5 years of age. (30)

Four consortia of birth and/or prenatal cohorts were also identified:

The International Childhood Cancer Cohort Consortium, comprising 11 cohorts, designed to study the role of various environmental and genetic exposures in the etiology of childhood cancer, has evaluated data related to approximately 700,000 children. (31)

The Environment and Childhood consortium, composed of 7 birth cohorts in Spain, aimed to evaluate the role of environmental pollutants in childhood growth and development, on the basis of data related to 3,768 children. (32)

The Consortium of Health-Oriented Research in Transitioning Societies, encompassing 5 of the largest birth cohorts located in low- and middle-income countries (Brazil, Guatemala, India, the Philippines, and South Africa), with the fundamental objective of providing high-quality scientific data on the early origins of chronic diseases and on human capital, has evaluated data related to approximately 22,840 children. (33)

The Nausea and Vomiting During Pregnancy Genetics Consortium, composed of 7 cohorts in Australia, Finland, Spain, Denmark, and the United Kingdom, designed to aggregate knowledge on genetic and environmental causes (with special attention to psychological causes) of nausea, vomiting, and hyperemesis in pregnant women, as well as on their incidence and severity, has evaluated data related to 25,830 women. (34)

TABLE 2. **Preconception, Prenatal, and Birth Cohorts by Region and Country**

REGION (TOTAL)	
Country	**No.**
Africa (n=4)	
Kenya	1
Mauritius	1
South Africa	2
The Americas (n=13)	
Brazil	4
Canada	1
Chile	1
Ecuador	1
Jamaica	1
United States	5
Asia (n=15)	
China	4
India	5
Israel	2
Japan	3
The Philippines	1
Europe (n=40)	
Belarus	1
Belgium	1
Czech Republic	1
Denmark	5
Denmark, Sweden, and Finland	1
England	7
Finland	4
France	2
Greece	1
Ireland	1
Norway	1
Scotland	2
Sweden	1
Switzerland	1
The Netherlands	5
Wales	1
England, Scotland and Wales	3
Isle of Man	1
United Kingdom (England, Scotland, Wales and Northern Ireland)	1
Oceania (n=12)	
Australia	10
New Zealand	2
Total	**84**

PRECONCEPTION, PRENATAL, AND BIRTH COHORT STUDIES AND EARLY-LIFE ORIGINS OF ADULT HEALTH AND DISEASE

Preconception, prenatal, and birth cohort studies provide a unique opportunity to assess the consequences of early life exposures on adult health and disease. By repeatedly assessing exposures and outcomes in individuals over time, such studies have the potential to identify early environmental exposures (physical, chemical, biological, social, or psychosocial factors) that influence health throughout life. (35) They allow the study of certain critical windows of time during which individuals are especially sensitive to their environment (critical development periods), (35) as well as the cumulative effects of exposures on health and disease throughout life. (36) Below are some examples of studies examining consequences of early-life exposures on later-life outcomes.

The investigation of the effects of the Dutch Hunger Winter of 1944-1945 on human development, particularly on mental performance, has become a classic study in the life course epidemiology literature, showing how a starvation diet during pregnancy influences subsequent health of the offspring. The information collected in the Dutch national psychiatric records made it feasible to examine psychiatric outcomes during adulthood among people exposed to hunger at different gestational periods during pregnancy. The best-known finding concerns the increased risk of schizophrenia among individuals exposed to the famine during the first trimester of gestation, (37) a finding that years later was replicated with data from the famine period faced by China between 1959 and 1961. (38)

Using data from ALSPAC, investigators reported that maternal prenatal fish consumption was associated with

TABLE 3. **Number of Preconception, Prenatal, and Birth Cohorts and Initial Number of Cohort Members, by Economic Status of the Respective Countries**

COUNTRY INCOME LEVEL[a]	COHORT STUDIES	ESTIMATED INITIAL COHORT MEMBERSHIP[b]
	N (%)	N
High	63 (75.0)	9,993,904
Middle	15 (18.0)	422,288
Low	6 (7.0)	46,139
Total	84 (100%)	10,462,331

[a] Classified by the income criterion established by the World Bank (updated in June 2017).
[b] Estimates obtained by calculating the sum of the numbers of initial members of each cohort reported in the cohort profile.

lower frequency of maternal depressive and anxiety symptoms, as well as lower frequency of intrauterine growth restriction and better neurocognitive child development. (39) Another example of an early environmental exposure that has an impact in later stages of life is breastfeeding. Studies using data from the Pelotas birth cohorts have reported that a longer duration of breastfeeding is associated with a higher level of education, higher IQ, and higher income in adulthood, (40) as well as a lower probability of presenting with severe depressive symptoms in adult life. (41)

The cumulative risk effect of early life exposures was examined using data from the 1958 British birth cohort. Investigators showed that child maltreatment (abuse and neglect) was associated with reduced adult socioeconomic outcomes and this was more extreme if there were multiple maltreatments. (42)

The long-term effects of environmental exposures may not be limited to individuals who have been exposed directly to the relevant exposure. (43)(44)(45) Emanuel et al (46) observed that the height of the grandmother (F0 generation) is a determinant of the birthweight of the mother (F1 generation), which in turn influences the birthweight of her child (F2 generation), establishing a chain of intergenerational associations. (46) The intergenerational approach is fundamental for understanding the intergenerational transfer of risk long after the initial environmental exposure has occurred.

WHY ARE NEW PRECONCEPTION, PRENATAL, AND BIRTH COHORT STUDIES NEEDED?

The epidemiologic, nutritional, and economic transitions experienced by most countries in the world justify the addition of new birth cohorts, mostly for measuring new exposures or exposures that have not been evaluated in previous decades, and for comparing associations between exposures and outcomes at different points in time and between cohorts. (47) The nature of the exposures can differ between higher-income and developing countries. For example, in higher-income countries, physical activity is predominantly leisure-related, whereas in poor countries, individuals engage in physical activity primarily on the way to work or in the working environment. (7) In low- and middle-income countries, certain exposures may have increased relevance because of the high prevalence of risk factors such as low birthweight, malnutrition, poverty, and violence. (7)(48) Finally, the confounding structures in middle- and low-income countries can be different from those found in high-income countries. (7) In exploring the confounding biases in the association between breastfeeding and IQ, Brion et al (49) found that socioeconomic status was a confounding variable in the England-based ALSPAC cohort (17) whereas no such bias was identified in the 1993 Pelotas cohort. (19) By comparing associations between exposures and outcomes in different contexts, it is possible to explore the probability of residual confounding and to improve causal inference. (49)

One important contribution of cohort studies is their ability to generate feedback for decision makers. Results of birth cohort studies can assist managers in monitoring population health indicators, analyzing health determinants, and strengthening health care and surveillance services. (20) In addition, the development of birth cohorts promotes improvements in the process of collecting and analyzing epidemiologic data, as well as in research and development of the scientific capacity of a country. (35)

CONCLUSION

Preconception, prenatal, and birth cohorts are extremely useful for the study of social and biological pathways linking early life and adult health and disease. The study of many biological, behavioral, and psychosocial processes that occur in childhood, adolescence and adulthood has been made possible through the analyses of environmental exposures from prenatal and birth cohort studies. However, the majority of such cohort studies have been conducted in high-income countries. Studying the relationship between exposure and disease and taking into account the specificities of each region makes it possible to adequately evaluate the mechanisms of risk and protection throughout a lifetime. The challenges that face cohort studies in the context of life course epidemiology include the availability of adequate data from environmental exposures at various stages

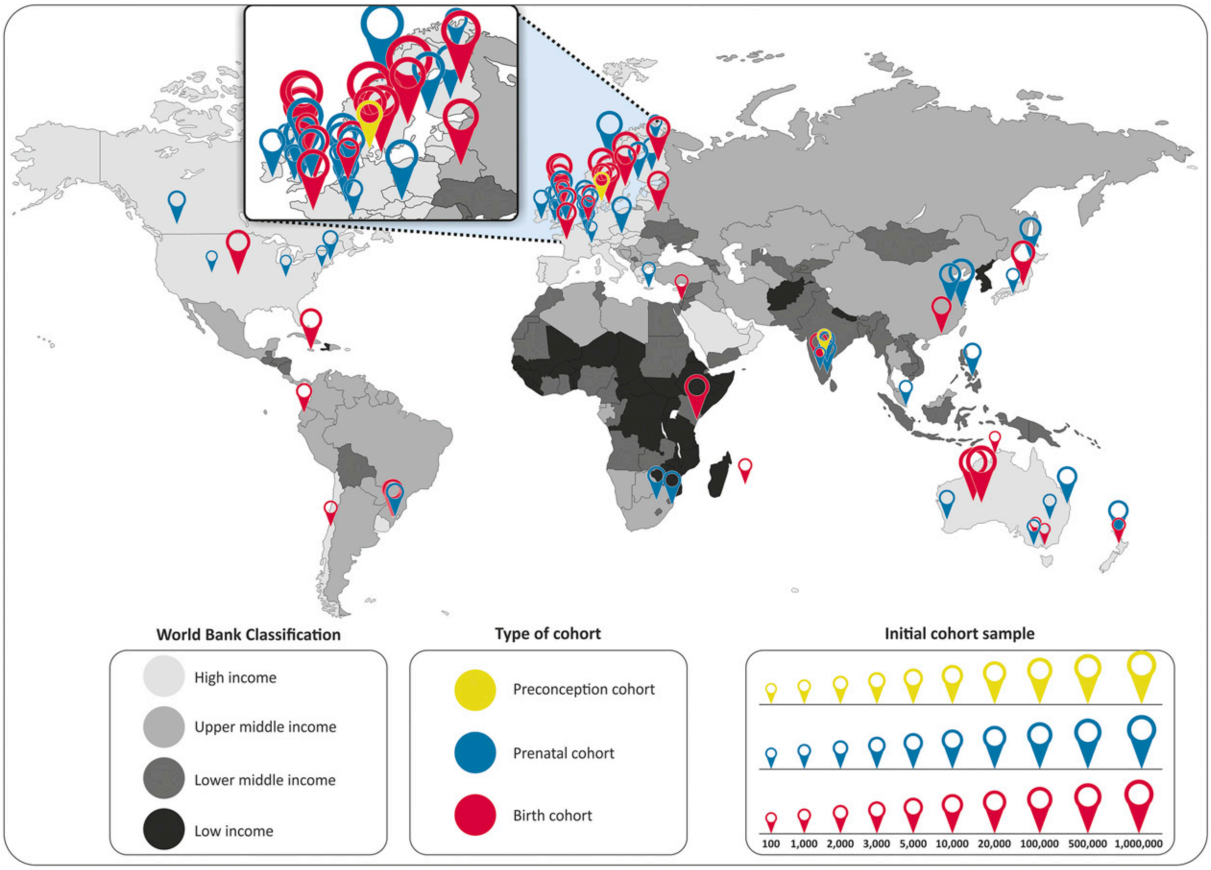

Figure 4. Map of the world showing the location of the preconception, prenatal, and birth cohorts identified. The size of each marker is proportional to the initial membership of each cohort, and the colors of the markers indicate whether the study involved a preconception, prenatal, or birth cohort. High-income, upper middle-income, and lower middle-income countries are identified by different shades of gray.

of the individuals' lives and the application of techniques capable of dealing with the complexity of the theoretical models involved. Sustainable financial support is mandatory to initiate and properly follow a preconception, prenatal, or birth cohort.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize a cohort study.
- Understand the strengths and limitations of cohort studies.

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Neonatal Acute Kidney Injury: Diagnosis, Exposures, and Long-term Outcomes

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Education Gaps

1. Neonatologists need to recognize the appropriate surveillance strategies for acute kidney injury (AKI) and the impact of fluid balance on neonatal outcomes of AKI.
2. Nephrologists should recognize normal preterm physiology and the impact of neonate-specific diseases and conditions on renal function.
3. There is a lack of consensus regarding a definition for neonatal AKI.
4. There is a gap in knowledge on long-term outcomes of neonates with AKI.

Abstract

Neonatal acute kidney injury is an underappreciated condition among patients cared for in the NICU. It may have both short- and long-term implications in this population. Improved surveillance during the initial hospitalization and during the first 2 decades of life has the potential to improve outcomes.

Objectives After completing this article, readers should be able to:

1. Identify risk factors for neonatal acute kidney injury (nAKI) and know when and how to screen high-risk neonates.
2. Explain how the presence of nAKI affects overall morbidity and mortality in the NICU.
3. Have increased awareness of the potential long-term implications of nAKI and know how to conduct surveillance for high-risk NICU graduates.

INTRODUCTION

Little is known about neonatal kidney function and injury, especially in preterm infants. This includes the paucity of data on how in utero and postpartum exposures affect renal function later in life. This review focuses on the current state of knowledge of neonatal acute kidney injury (nAKI), including how renal

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ABBREVIATIONS

AKI	acute kidney injury
AWAKEN	Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates
BP	blood pressure
CKD	chronic kidney disease
CPAP	continuous positive airway pressure
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
GFR	glomerular filtration rate
HIE	hypoxic-ischemic encephalopathy
HTN	hypertension
KDIGO	Kidney Disease: Improving Global Outcomes
nAKI	neonatal acute kidney injury
NIH	National Institutes of Health
PDA	patent ductus arteriosus
SGA	small for gestational age
VLBW	very low birthweight

development may be affected by prematurity and AKI, the diagnosis of and surveillance for nAKI, the risk of long-term chronic kidney disease (CKD) after nAKI, and emerging data from a multicenter retrospective study of nAKI. (1)(2) The goal of this article is for readers to gain a better appreciation of the issues, knowledge gaps, and opportunities for the future in the field of nAKI.

There are few other places in the era of modern medicine that have gone through such an evolution as has occurred in the NICU. Therapies such as continuous positive airway pressure (CPAP), surfactant, maternal corticosteroids, extracorporeal membrane oxygenation (ECMO), and cooling protocols have existed for only 30 to 40 years; some therapies have been standard of care for an even shorter period. It is clear that today, neonates admitted to the NICU who in another era would not have been resuscitated or who would have died within a matter of hours are now surviving to adulthood. Of nearly 4,000,000 live births in 2015 in the United States, 9.6% were born at less than 37 weeks' gestation: 0.7% were 27 weeks' gestation or less and 2.1% were 28 to 33 weeks' gestation. (3) Thus, the population graduating from the NICU is not small. Amazingly, most infants born weighing between 500 and 1,500 g survive to discharge (90%), and 60% leave with no major neonatal morbidity. (4) However, the long-term consequences of a critically ill beginning are far less clear. (5) There is emerging evidence from the basic science and clinical arenas to suggest that both prematurity and the required lifesaving therapies may have serious long-term consequences for kidney health.

Although much work has been dedicated to advancing the field of AKI in adults and children, there are still many areas in the field of nAKI that remain unclear or unanswered. This may be due in part to the silos of neonatology and pediatric nephrology. Neonatologists care for the "whole" infant, balancing all organ systems; few neonatologists have expertise in the area of neonatal kidneys. Most neonatologists focus on the infant population only, many of whom have little follow-up with patients after discharge from the NICU or after the newborn period. Pediatric nephrologists focus only on renal physiology and are more familiar with issues in older pediatric patients.

We identified similarities and differences in these knowledge gaps in a survey taken by neonatologists and nephrologists that was published in 2017. (3) Herein we present cases that are similar to the published ones highlighting the unique features of nAKI and summarizing the current state of knowledge in this field. Rectifying these information gaps will take dedicated collaborations between neonatologists and pediatric nephrologists.

CLINICAL SCENARIO: BABY A

Baby A was born to a 28-year-old woman with preterm rupture of membranes who received betamethasone for fetal pulmonary maturation and 3 doses of indomethacin for tocolysis. The female infant was delivered at 25 2/7 weeks' gestation, weighing 650 g. She was intubated at birth, received surfactant, and was extubated on day 2 of age. She received 2 days of ampicillin and gentamicin during a sepsis evaluation. Gentamicin levels were not obtained and serum creatinine level was not included in the routine electrolyte panels. Later in the first week after birth, a clinically significant patent ductus arteriosus (PDA) was diagnosed and treated with indomethacin. The serum creatinine level was 0.8 mg/dL (70.7 μmol/L) before starting indomethacin therapy and peaked at 1.2 mg/dL (106.1 μmol/L) after the third dose. Concomitantly, the urine output decreased during treatment but remained greater than 1.0 mL/kg per hour. Following the course of indomethacin, the serum creatinine level decreased to 0.4 mg/dL (35.4 μmol/L).

The scenario described in Baby A is very common, one that all neonatologists encounter, and unlikely to involve a nephrologist. This is an extremely low birthweight infant exposed both in utero and after birth to at least 2 drugs that may be nephrotoxic. A PDA can result in decreased renal blood flow (as well as decreased splanchnic blood flow) and can sometimes be treated if there are signs that it is "clinically significant."

There are at least 2 potentially significant risk factors for impaired renal function highlighted in this scenario: extreme prematurity and the presence of a PDA treated with a nephrotoxic drug. In addition, we need to distinguish between impaired renal function and acute injury in this population.

Whether a consequence of treatment (ie, indomethacin) or due to the indication for the therapy (ie, PDA), the question remains, "Did this baby have AKI?" In this case, is the rise in creatinine level a sign of AKI or is it just an indication that the indomethacin is acting as predicted, causing vasoconstriction that is not restricted to just the ductus? If solely vasoconstriction related, does that impact the developing kidney, causing damage, or is it just a change in the renal hemodynamics? Given incomplete nephrogenesis, is the change in creatinine level a surrogate for low nephron numbers?

Definition of AKI

AKI is defined as an abrupt decline in renal function that results in a derangement of fluid balance, electrolytes, and waste products. Both adult and pediatric nephrologists are attuned to the impact of AKI because it is clearly associated with poor outcomes. In adults, AKI is independently associated with increased risk of death, length of hospitalizations, and cost. (6) In children, the situation is similar: AKI is independently associated with increased risk of death, ventilator days, and length of stay. (7) However, there are limited data in neonates. There is currently no standard of care for renal function surveillance in neonates. Renal function, measured by serum creatinine level, often is a part of an electrolyte panel for neonates and is not likely to be assessed independently of an electrolyte panel.

There have been many definitions for AKI in the adult, pediatric, and neonatal literature. Arbitrary cutoff levels of serum creatinine greater than 1.5 mg/dL (>132.6 μmol/L) or greater than 2.0 mg/dL (>176.8 μmol/L) (8) have been used in neonates, in addition to gestational age cutoff points (9) and rate of decline in term neonates. (10) However, the most often used categorical definition for nAKI that has been independently associated with mortality and length of stay is the modified neonatal Kidney Disease: Improving Global Outcomes (KDIGO) definition. (11) This definition accounts for a change in serum creatinine level from a previous base, includes urine output criteria, and has 3 stages accounting for AKI severity (Table 1).

Serum creatinine level is imperfect as a surrogate for renal function. It is a late functional marker that takes 24 to 48 hours to change after injury. Serum creatinine level is particularly problematic for very small neonates with low muscle mass and provides no specificity for the type of injury. Depending on the type of assay used, there can be interfering substances. Specifically in neonates, the creatinine level detected at the time of birth reflects maternal renal function and can be elevated in the neonate in the setting of maternal renal disease or placental dysfunction. The modified neonatal KDIGO definition does not address the situation in which the serum creatinine level does not decrease and neonates may be misclassified. Often in immature neonates, urine output can be maintained despite significant injury. There are clearly many limitations to the neonatal AKI definition; however, at a 2013 National Institutes of Health (NIH) workshop, experts in the field agreed that despite its limitations, the KDIGO definition for nAKI was the most appropriate definition. (12)

Using the categorical definitions, the rates of nAKI range from 16% to 71%. (13) The incidence of AKI in preterm infants ranges from 18% to 40% and is independently associated with mortality and length of stay. (14)(15)(16) An understudied but large population of neonates includes those born late preterm. (17) The only study to examine this population using the KDIGO definition for nAKI showed that 16% developed AKI. (15) Congenital anomalies, including heart defects and diaphragmatic hernias, and perinatal asphyxia are admission diagnoses of term neonates that confer a high risk for developing AKI, with a prevalence rate ranging from 38% to 71%. (18)(19)(20)(21)(22)(23)

Renal Development

The neonate in scenario A was born extremely preterm, a factor that may exacerbate potentially nephrotoxic episodes because kidney development was incomplete. The development of nephrons in humans begins at approximately 9 weeks' gestation (24)(25) and is complete at approximately 36 weeks' gestation. (26) A full-term neonate has the final nephron endowment at birth. The kidney continues a maturational process for nearly 2 years, at which time adult glomerular filtration rate (GFR) is established. Important in the setting of prematurity, the third trimester is a very active

TABLE 1. **Neonatal Acute Kidney Injury Based on KDIGO Classification (11)**

STAGE	SERUM CREATININE	URINE OUTPUT
0	No change in sCr *or* rise <0.3 mg/dL (<26.5 μmol/L)	≥0.5 mL/kg per hour
1	sCr rise ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h *or* sCr rise ≥1.5–1.9 times the reference SCr[a] within 7 d	<0.5 mL/kg per hour for 6 to 12 h
2	sCr rise ≥2–2.9 times the reference sCr[a]	<0.5 mL/kg per hour for ≥12 h
3	sCr rise ≥3 times the reference SCr[a] *or* sCr ≥2.5 mg/dL (≥221 μmol/L)[b] *or* receipt of dialysis	<0.3 mL/kg per hour for ≥24 h *or* anuria for ≥12 h

KDIGO=Kidney Disease: Improving Global Outcomes, sCr=serum creatinine.
Differences between the proposed neonatal AKI definition and KDIGO include:
[a] *Reference sCr is defined as the lowest previous sCr value.*
[b] *An sCr value of 2.5 mg/dL (221 μmol/L) represents less than 10 mL/min/1.73 m²*.

time for nephrogenesis, with up to 60% of nephron development occurring during this window. (27) Nephrons do not regenerate, (28) and once the self-renewing population of metanephric mesenchyme has been depleted, new glomeruli cannot be created. Please refer to the article by Yanik et al in a 2015 issue of *NeoReviews* for a more complete review of renal development. (29)

It is commonly taught that a human has approximately 1,000,000 nephrons per kidney. Although this is a fundamentally true statement, it is based on relatively few published studies, with averages that range from 617,000 to 1.4 million. (30)(31)(32) It is also important to understand that nephron number is highly variable among humans (210,000 to 2,700,000). (31) Many factors can affect an individual's nephron number, including sex, race, comorbid conditions, and even birthweight (Table 2). In 2006, Australian investigators examined the association of birthweight and nephron number and found that a 1-kg increase in birthweight conferred nearly 200,000 additional nephrons. (56) However, nephron number can currently be assessed postmortem only because stereologic techniques are used to estimate glomerular number. (57) A kidney biopsy alone is insufficient to determine nephron number.

Postnatal Nephrogenesis

Little is known about postnatal nephrogenesis after preterm birth. Two descriptive histologic autopsy studies have shown that glomerulogenesis does seem to continue after preterm birth, but the window of nephrogenesis may be shortened and abnormal. An autopsy study of a cohort of gestational age–matched preterm neonates from Australia showed acceleration of the maturation of the kidney and a smaller nephrogenic zone. (58) The investigators described structurally abnormal-appearing glomeruli in their cohort. A second study by investigators at the University of Miami demonstrated ongoing glomerulogenesis for 40 days after birth in infants born weighing less than 1,000 g, but their kidneys had fewer layers of glomeruli than their full-term counterparts. (8) This study also took into account the role of AKI, and infants who had a sustained serum creatinine level greater than 2.0 mg/dL (>176.8 μmol/L) had fewer layers of glomeruli than those without AKI. If nAKI independently leads to fewer glomeruli, then it is not surprising that the preterm population is at risk for CKD.

Commonly Used Nephrotoxic Medications

As described in scenario A, nonsteroidal anti-inflammatory drugs are another lifesaving and commonly used class of

TABLE 2. **Factors Affecting Nephron Number During In Utero and Early Neonatal Development**

FACTORS AFFECTING NEPHRON NUMBER	MECHANISM OF ACTION	REF. NO.(S)
Caloric restriction	Reduced nephron number	33, 34
Protein restriction	Reduced nephron number with increased apoptosis and reduced progenitor cells	35–37
Iron deficiency	Reduction in hepatic mobilization of vitamin A	38
Vitamin A deficiency	Reduced ureteric bud branching Reduced nephron number	39
Vitamin D deficiency	Increased nephron number Potential mechanisms: active (1,25-OH) vitamin D stimulates cell differentiation and inhibits proliferation or active vitamin D negatively regulates renin expression, increased levels of angiotensin II could stimulate nephrogenesis	40–44
Aminoglycosides	Reduced nephron number	45, 46
Nonsteroidal anti-inflammatory drugs	Reduced nephron number	47
Corticosteroids	Exposing metanephros culture media to dexamethasone for 2 d decreased the number of ureteric buds, resulting in fewer nephrons even when dexamethasone was removed	48–50
Tobacco	Reduced nephron number	51
Ethanol	Reduced nephron number	52, 53
Hyperglycemia	Metanephros development is impaired by hyperglycemia	54, 55

medications to treat or prevent PDA. These drugs are nephrotoxic largely due to their vasoconstrictive properties. In a single-center study, Rhone et al (59) reported that approximately 50% of very low-birthweight (VLBW) infants received indomethacin, with nearly 5 days of use and an average cumulative dose of 1.0 mg/kg. In rodents, the administration of indomethacin during the window of nephrogenesis resulted in the formation of fewer nephrons, and in a premature baboon model, ibuprofen reduced the nephrogenic zone. (58)(59) Possibly more alarming was a publication by Kent et al in 2012 (60) demonstrating an increased number of podocytes in the urine of infants receiving indomethacin. The podocyte is a terminally differentiated cell in the glomerulus that supports the glomerular filtration barrier, and permanent glomerular damage (focal segmental glomerulosclerosis) occurs when there is a reduction of podocytes.

CLINICAL SCENARIO: BABY B

Baby B was born at 30 weeks' gestation after a pregnancy complicated by maternal pregnancy-induced hypertension (HTN) and severe intrauterine growth restriction. The pregnant woman was treated with betamethasone and magnesium sulfate in anticipation of an early delivery. The male infant weighed 890 g at birth and was assigned Apgar scores of 7 and 8 at 1 and 5 minutes, respectively. He was started on nasal CPAP but required transient intubation for surfactant at 6 hours of age. On day 7, his serum creatinine level was 0.3 mg/dL (26.5 µmol/L). Although the baby did well initially, at 14 days of age he began to have significant apnea and bradycardia requiring intubation. At the time of intubation, he had a mixed respiratory and metabolic acidosis. His creatinine level was 0.6 mg/dL (53.0 µmol/L), and his urine output had decreased to less than 0.5 mL/kg per hour. A sepsis evaluation was performed, and gentamicin and ampicillin were administered. Because the baby was hypotensive, he received a normal saline bolus and was started on dopamine therapy. The next day his creatinine level was 0.75 mg/dL (66.3 µmol/L). Within 24 hours, the blood culture was reported positive for Staphylococcus epidermidis *resistant to ampicillin, so this was stopped and vancomycin alone was administered for 10 days. The baby's creatinine level decreased to 0.6 mg/dL (53.0 µmol/L) at the completion of the course of vancomycin and 0.3 mg/dL (26.5 µmol/L) at discharge.*

> Sepsis is a common concern in the NICU population. Although most patients receive brief courses of nephrotoxic drugs, predominantly aminoglycosides and vancomycin, during sepsis evaluations, true septicemia occurs and warrants a prolonged course of treatment. In scenarios A and B, it is not clear whether the condition (PDA or sepsis) or its treatment (prostaglandin inhibitor or antibiotics) is the more important risk factor for renal injury or whether the 2 are additive or synergistic.
>
> Intrauterine growth restriction affects a significant proportion of patients in the NICU. The etiologies of impaired growth are numerous, including maternal and fetal factors. How these factors affect kidney development and ultimate function remains to be fully elucidated.

NICU Exposures that Influence Renal Development

Patient susceptibility factors and kidney stressors influence the risk of AKI. Patient susceptibility factors have been identified in adult studies, but many apply to neonates, including diabetes in the form of maternal exposure, congenital anomalies of the kidney, malnutrition, and birthweight. Nevertheless, even the least susceptible patients can have kidney injury if the stress is significant. Common kidney stressors in the NICU include volume depletion, sepsis, shock, hypoxemia, nephrotoxic medications (61) (including vancomycin, aminoglycosides, nonsteroidal anti-inflammatory drugs, iodinated contrast), and invasive mechanical ventilation. Animal and human data demonstrate how many exposures in the NICU may affect renal development. It is critical to identify these factors to improve short- and long-term outcomes, to preserve as much as possible of the very short window of nephrogenesis.

As described in scenario B, aminoglycosides are commonly used in the NICU because they are excellent antimicrobial agents to treat neonatal sepsis despite their nephrotoxic potential. In a single-center study, nearly 86% of the VLBW neonates received an aminoglycoside, with an average of 10 days of use and an average cumulative dose of 32 mg/kg. (59) These drugs accumulate in the cortex and can be toxic because of this accumulation despite therapeutic systemic levels. It is proposed that some of the infants with the lowest gestational age might be "protected" from aminoglycosides owing to their immature endocytic transport system in the proximal tubule, but further work needs to be done to confirm this hypothesis. Animal data would suggest that the aminoglycoside effect on the kidney may be present despite an immature transport system. In a rodent study in which gentamicin was given daily to pregnant rats beginning midway through the gestation, the offspring had few glomeruli at birth and developed glomerulosclerosis during adulthood; it is unclear whether the glomerulosclerosis is a direct impact of the low nephron number at birth or a long-term consequence of the drug. (45)(62)

However, not all unique exposures in the NICU may increase the risk of nAKI. Recently published data suggest that early treatment with caffeine may be protective and prevent or ameliorate nAKI in the preterm population. (63) In this single-center retrospective observational study, infants born before 32 weeks' gestation who received caffeine had a significantly lower rate of early AKI compared with those not receiving caffeine (11.5% vs 31.4%; $P < .01$). (63) In addition, the caffeine-exposed group experienced significantly less severe nAKI ($P < .01$). Of note, in comparing the percentage of stage 3 AKI, the no caffeine group had 6 times the rate of stage 3 AKI compared with the caffeine group.

Neonatologists are well aware of the benefits of vitamin A regarding lung development. However, the benefit of vitamin A also extends to the developing kidney. Vitamin A may modulate nephron number via interaction with the RET receptor. Vitamin A deficiency may downregulate this receptor, resulting in decreased branching of ureteric bud tips. The relationship of plasma retinol levels and nephron number is demonstrated in a French study that showed that plasma retinol levels were highly correlated to lower nephron numbers in rats in a dose-dependent manner. (64) Vitamin A deficiency rarely occurs in developed countries but is common in many underdeveloped countries, affecting nearly 20 million pregnant women globally. Intriguing data have been published demonstrating smaller kidney volumes in offspring of pregnant women with vitamin A deficiency, suggesting that vitamin A status may also affect renal development in humans. (65)(66)

CLINICAL SCENARIO: BABY C

Baby C was born at 41 3/7 weeks' gestation weighing 4,850 g to a 38-year-old woman with uncontrolled gestational diabetes. Shoulder dystocia occurred, and the male infant required extensive resuscitation. He was assigned Apgar scores of 1 at 1 minute and 3 at 5 minutes. The arterial cord gas had a pH of 6.9 and a base deficit of 18. He was resuscitated and underwent therapeutic hypothermia. He required vasopressors to maintain an appropriate blood pressure (BP). Macroscopic hematuria was noted, followed by anuria at 30 hours of age. He remained anuric at 48 hours of age and was approximately 20% over birthweight. The infant's creatinine level steadily rose to a peak of 3.0 mg/dL (265.2 μmol/L) at 48 hours of age, then very slowly decreased such that by discharge at 3 weeks of age it was 1.0 mg/dL (88.4 μmol/L).

This infant is term and experienced an acute perinatal insult resulting in hypoxic-ischemic encephalopathy (HIE). He also clearly experienced AKI as manifested by both anuria and elevation in the serum creatinine level. What is not necessarily as clear is the long-term implication of this kidney injury and whether the long-term implications vary depending on the type of patient population.

AKI and HIE

Multiple organ failure is commonly associated with HIE. Both in the era before therapeutic hypothermia and after adoption of cooling strategies to ameliorate neurodevelopmental impairment after acute perinatal asphyxial events, AKI remains prevalent. This association may be due to a common etiology or AKI may exacerbate organ system injury via inflammatory mechanisms, as suggested by Sarkar et al. (67) Because these investigators were able to predict the presence of magnetic resonance imaging abnormalities from their participants' AKI status, the recognition of nAKI may suggest the need for heightened long-term neurodevelopmental follow-up.

As discussed previously herein, the diagnosis of AKI in neonates presents unique challenges. Gupta et al (10) suggest that in the asphyxiated newborn, the rate of decline in serum creatinine level during the first 5 to 7 days after birth is a feasible means of identifying clinically significant AKI. Neonates whose creatinine levels did not fall required more respiratory support and vasopressor treatment, had an increased average fluid balance, and had a longer length of stay compared with those whose creatinine levels declined within the first week.

Defining CKD

A critically important clinical question is: Will Baby C develop CKD? Most nephrologists would say that this child is at significant risk for the development of CKD. However, in a recent survey, neonatologists were less convinced. (68) Nephrologists agree that there is a relationship between AKI and CKD, but where AKI is on the causal pathway is still debated (Table 3). Many nephrologists believe that AKI results in a reduction of nephrons due to the AKI event and that this reduction of nephrons leads to CKD. Others believe that AKI reflects a "lack of reserve" or a lower endowment of nephrons, which eventually would have manifested as CKD later in life. Regardless of the pathway, there is an association between AKI and CKD, and this relationship may be even more important than in adults because neonates have a far longer life to live with the burden of CKD. In the most simple of definitions, CKD is too few nephrons to do the work of the kidney. CKD is independently associated with death and cardiovascular disease. When stratified by stage of CKD, there is a stepwise increased risk of death, cardiovascular event, or hospitalization. (77) CKD is expensive (78) and a burden to the health-care system, patients, and families.

The 5 stages of CKD are defined by GFR, most commonly estimated by serum creatinine concentrations. Stage 1 is

TABLE 3. **Risk Factors for Development of CKD in NICU Graduates**

FACTORS AFFECTING THE DEVELOPMENT OF CKD	POTENTIAL MECHANISMS OF ACTION	REF. NO.(S)
Low birthweight	Unclear, but may be secondary to lower nephron number	27, 69, 70
Preterm birth	Nephron maldevelopment, reduced nephron number, AKI, nephrotoxic exposure	58, 71–74
Perinatal asphyxia	Hypoxia	20
Congenital heart disease	Hypoxia, abnormal renal hemodynamics	75, 76

AKI=acute kidney injury, CKD=chronic kidney disease.

normal kidney function with a GFR greater than 90 mL/min per 1.73 m² but with some "kidney damage." For example, a child with a single kidney and an estimated GFR (eGFR) of 110 mL/min/1.73 m² has stage 1 CKD. There is radiologic evidence of renal agenesis, but this child's renal function is normal. There are a few notable limitations with this construct for CKD for neonates. First, there is a developmental increase in GFR where adult GFR is reached at age 2 years, making the assessment for CKD difficult in neonates, infants, and young children. Second, GFR is a functional metric of the whole kidney and is defined by the GFR of each nephron multiplied by the number of nephrons in the kidney. When nephron number is low, the remaining glomeruli hypertrophy to increase the single-nephron GFR; therefore, surface area to complete filtration is maintained despite an absolute fewer number of nephrons. Third, most estimates of GFR are calculated using serum creatinine. This is particularly problematic in the neonate, infant, and young child because muscle mass is small. Last, creatinine is secreted into the urine, overestimating the true GFR.

In 2009, White and colleagues (79) published a meta-analysis of 31 studies showing that low birthweight conferred a 73% increased risk of developing adulthood CKD. Even more concerning was that this risk was present not only in adults but could also be detected in childhood. In 2014, Hsu and colleagues (80) showed that the odds of developing CKD were nearly 3 times higher in individuals born weighing less than 2,500 g.

Besides GFR changes, renal dysfunction can manifest with higher BP and proteinuria. Investigators at Eastern Virginia Medical School used the NHANES database to analyze the effect of birthweight on long-term renal outcomes in nearly 5,000 adolescents by examining eGFR, BP, and albuminuria. (81) Low-birthweight and VLBW adolescents more frequently had elevated BPs and decreased eGFR; the VLBW group had a 2.5 times greater odds of developing a lower GFR.

Small single-center cohort studies with various renal dysfunction outcome metrics continue to be published and provide insight into the best ways to assess the renal health of the NICU population. A Japanese study showed that 38% of 5-year-olds born VLBW had an eGFR less than 90 mL/min/1.73 m² and higher urinary angiotensinogen levels. (82) Similarly, a Polish study looking at approximately 7-year-olds born extremely low birthweight had smaller kidney sizes, higher BPs, and higher serum cystatin C levels. (83) These studies suggest that serum cystatin C may be a better marker to detect early renal dysfunction than serum creatinine to assess renal health in follow-up. Neither of the aforementioned studies accounted for AKI.

During the past year, 2 publications have examined the effect of AKI on long-term renal health in the VLBW population. Bruel et al (84) used a gestational age cutoff criteria for AKI and prospectively matched kids with AKI with those who did not have AKI. They found that the children with AKI had smaller kidneys but no difference in eGFR using creatinine levels. However, 23% of their cohort had an eGFR less than 90 mL/min/1.73 m². In a smaller study published by Harer et al in 2017, (85) the modified KDIGO criteria were used to define AKI. In this study, the VLBW infants exposed to AKI had a 4.5 times higher risk of a composition outcome of elevated BP, proteinuria, or eGFR less than 90 mL/min/1.73 m² estimated using cystatin C levels.

There are several groups of full-term neonates in which AKI has been accounted for as a risk factor for the development of CKD. In 2014, a group from the Netherlands described the long-term renal follow-up of children who were exposed to ECMO. (20) Of the 423 participants who were exposed to ECMO from 1992 through 2002, the researchers assessed 169 at the average age of approximately 8 years. Nearly one-third of these children had some evidence of renal dysfunction, including an eGFR less than 90 mL/min/1.73 m², HTN, or proteinuria. Moderate or severe

AKI was the only predictive factor in neonates who later developed CKD or HTN, with a risk that was 4 times as high.

Nearly 50% of adults with congenital heart disease develop CKD. (75) Investigators at Cincinnati Children's Hospital examined a cohort of neonates who required cardiopulmonary bypass for long-term kidney injury. (76) The researchers used traditional CKD measurements such as eGFR, albuminuria, and HTN but also examined their urine to determine whether there were structural differences in those exposed to AKI. The mean follow-up was 7 years, and there was no difference in the traditional markers of renal disease between the AKI and no AKI groups. However, there were striking and sustained differences in structural urinary biomarkers, with an increased amount of interleukin-18 and L-fatty acid binding protein in the urine of the AKI group.

Kidney disease is a public health epidemic. Because of very high individual and societal costs of treatment, prevention is the most effective approach to sustainably address the mounting global burden of kidney disease. Therefore, it is the aim of all nephrologists to reduce the risk of progression of renal disease, but there are currently no guidelines that describe which neonates require follow-up, when to institute this screening and educational visit, or the best approach to screen for CKD.

Screening for CKD

The KDIGO is a global organization that is developing and implementing evidence-based clinical practice guidelines in kidney disease. The generalized guidelines designed for follow-up in adults advocate for follow-up 3 months after the AKI. (86) Most would agree that follow-up for neonatal AKI should occur, but it is unlikely that the 3-month timeframe is an optimal follow-up period, particularly because GFR is not established until 2 years and it is very difficult to interpret GFR criteria in this young cohort. Primary care physicians may be able to obtain a child's gestational age and birthweight, but a "history of AKI in the neonatal period" is not often included in discharge summaries. (15) AKI must first be recognized and then must be communicated.

To date, the American Academy of Pediatrics does not have any guidelines for screening for CKD aside from a recommendation that children with a history of prematurity, VLBW, or "other" neonatal conditions have their BP measured before 3 years of age. The American Academy of Pediatrics does highlight prematurity as a potential high-risk group for HTN in the 5th Report of the Clinical Practice Guidelines for high BP. (87) Children at higher risk for CKD are those with early HTN because this may be a clinical indicator of low nephron number. There is evidence that preterm infants, irrespective of the presence or absence of nAKI, have abnormal BP parameters early in childhood. In a Swedish national population-based cohort, 44% of children who were born with extremely low birthweight had office systolic BP readings greater than the 90th percentile at age 2.5 years compared with age, sex, and height standards. (88) Ambulatory BP monitoring also reveals that preterm infants may be at risk for abnormal circadian BP patterns. (89) The diagnosis and appropriate management of HTN may be an important target to protect the kidney and slow or halt the potential progression of CKD.

Abnormal growth parameters may also be associated with CKD. Children with CKD can have impaired linear growth even when their GFR is only mildly to moderately impaired. Given the potential for poor linear growth and reduced muscle mass in preterm infants, estimating GFR by serum creatinine level may represent a further challenge for screening for CKD in this population. In addition to earlier screening of growth parameters, adolescents are in another period of rapid growth that may unmask renal dysfunction.

If at any of these screening visits the child has a BP at the 95% level or higher, microalbuminemia or proteinuria, an elevated creatinine or cystatin C level, or abnormal renal ultrasonography findings, he or she should be referred to a pediatric nephrologist. In addition, as the child transitions to adult care, it will be important to alert the new primary care provider of important early life events that may put them at risk for more rapidly deteriorating renal function as they age. In 2013, an algorithm was proposed to address who should be screened for CKD and when (Fig).

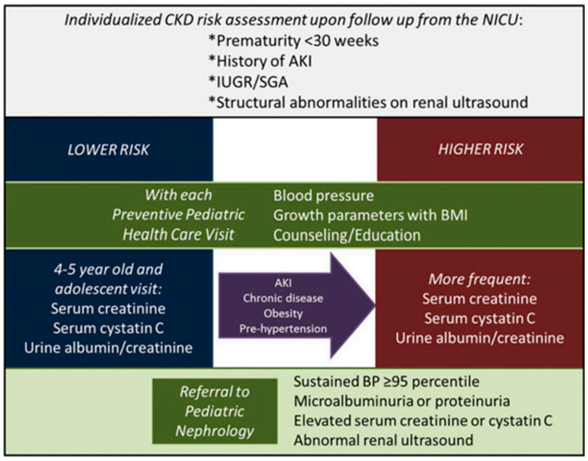
Individualized CKD risk assessment upon follow up from the NICU:
*Prematurity <30 weeks
*History of AKI
*IUGR/SGA
*Structural abnormalities on renal ultrasound
LOWER RISK
HIGHER RISK
With each Preventive Pediatric Health Care Visit
Blood pressure
Growth parameters with BMI
Counseling/Education
4-5 year old and adolescent visit:
Serum creatinine
Serum cystatin C
Urine albumin/creatinine
AKI
Chronic disease
Obesity
Pre-hypertension
More frequent:
Serum creatinine
Serum cystatin C
Urine albumin/creatinine
Referral to Pediatric Nephrology
Sustained BP ≥95 percentile
Microalbuminuria or proteinuria
Elevated serum creatinine or cystatin C
Abnormal renal ultrasound

Figure. Suggested algorithm for the assessment of NICU graduates at risk for chronic kidney disease (CKD).
AKI=acute kidney injury, BMI=body mass index, BP=blood pressure IUGR=intrauterine growth restriction, SGA=small for gestational age.

Although there is no specific medication or therapy to preserve renal health, there are educational opportunities to reduce the risk of renal dysfunction progression. The avoidance of unhealthy lifestyles may be beneficial along with education on the ill effects of obesity, HTN, smoking, nephrotoxic drugs, urinary tract infections, and a high sodium diet.

CURRENT EFFORTS TO BETTER UNDERSTAND nAKI, INCLUDING DIAGNOSIS, TREATMENT, AND LONG-TERM PROGNOSIS

The NIH organized a workshop in 2013, bringing together nephrologists and neonatologists with leadership from the National Institute of Diabetes and Digestive and Kidney Diseases. In particular, much attention was given to the role of AKI as an antecedent for CKD. Several key elements were outlined that are needed to conduct a long-term follow-up study (Table 4).

One of the outcomes of this workshop was the formation of the Neonatal Kidney Collaborative with the specific goal of neonatologists and pediatric nephrologists working together to better understand AKI in neonates. The goal of the collaboration is to improve the understanding and ultimately the lives, health, and well-being of newborns at risk for kidney disease by assembling an international multidisciplinary team that can perform clinically relevant hypothesis-driven studies. Multicenter data could then be used to answer critical gaps in knowledge with the long-term goal of improving outcomes for neonates at risk for kidney disease.

The first endeavor for the Neonatal Kidney Collaborative was the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study. This was a retrospective cohort study involving 24 sites. Each participating site was asked to review all NICU admissions from January 1 through March 31, 2014. Patients in the NICU were eligible if they received at least 48 hours of intravenous fluids as their source of fluids and nutrition. Infants were excluded if they were admitted to the NICU more than 2 weeks after birth, required congenital heart disease repair before 7 days of age, died within 48 hours of admission, or had a known lethal chromosomal anomaly. Data collection included basic demographics (maternal and neonatal), delivery interventions, daily physiologic parameters during week 1 (weight, BP, intake and output, respiratory support, clinically obtained laboratory results), weekly "snapshots" (as during week 1, but limited to only 1 day per week), discharge information (growth parameters, final diagnoses, relevant discharge medications, need for renal replacement therapy [dialysis]), and all serum creatinine values.

Initial analyses focused on the epidemiology of nAKI, identification of risk factors that may predispose newborns

TABLE 4. **Issues Raised and Addressed at the National Institutes of Health Workshop on Neonatal AKI**

• *What population should be studied?*
An entire cohort of hospital survivors with and without AKI?
Neonates with known AKI, regardless of underlying conditions or cause of AKI?
Inclusion of controls is important so that true incidence, risk factors, and relative risk can be assessed
• *Sample size*
Estimates of 1,000–1,500 survivors may be needed to provide sufficient power
It would take 12–18 centers, each enrolling 40 patients per year for 2 y to achieve this number
• *Exposure variables*
Frequent determination of serum creatinine level
Careful measurement of urine output
Urine biomarkers
• *Outcome measures*
Primary: glomerular filtration rate and blood pressure
Secondary: microalbuminuria, renal ultrasonography, evaluation of tubular function, growth and growth velocity, neurodevelopmental assessments
Exploratory: new imaging techniques, biomarkers, renal functional reserve assessment
• *Study duration*
Serial evaluations until transition to adult care clinicians (17–18 years of age)
• *Challenges*
Recruitment and retention
Close contact with families; buy-in from families
Inclusion of specific populations that may be underrepresented in clinical studies (low socioeconomic status in particular)
Collection of meaningful, accurate data
Proper measurement of blood pressure
Standardized collection of blood and urine samples
Standardized measurement of glomerular filtration rate
• *Ethical issues*
In pediatric studies, if a procedure does not provide any direct benefit, it must be low risk or an IRB will not approve it

Continued

TABLE 4. **(Continued)**

• *Opportunities*
Several networks currently exist (Neonatal Research Network, Pediatric Trials Network, Vermont Oxford Network, Canadian Neonatal Network, Pediatrix, and the Pediatric Heart Network), but neonatal AKI has not been a focus for any of these groups in the past
Each of the networks has clear strengths and the potential to contribute to our knowledge in this area

AKI=acute kidney injury, IRB=institutional review board.

to AKI, and the contribution of fluid balance to overall morbidity, mortality, and likelihood of AKI. Not surprisingly, the incidence of AKI varied as a function of gestational age. Neonates of 22 to 29 weeks' gestation comprised only 14% of the neonates (n = 273), but nearly half had AKI. Of the 916 neonates of 30 to 35 weeks' gestation, approximately 18% had AKI, and of the 833 neonates of 36 weeks' gestation and older, approximately 37% had AKI. These incidences are approximate because this was a retrospective study and data collection, especially creatinine levels and complete intake and output data needed to diagnose AKI was not complete for all neonates. However, the data do highlight the significant proportion of infants at risk for AKI. More importantly, the data support the hypothesis that the presence of AKI has a significant effect on morbidity and mortality. After adjustment for a variety of confounders, infants with AKI were 4 times more likely to die, and their length of stay in the NICU was almost 9 days longer. Moreover, the more severe the injury, the higher the mortality rate and the longer the length of stay among the survivors.

We hypothesized that identifiable maternal, perinatal, and neonatal characteristics could predict neonatal AKI. Indeed, neonates born at outside facilities, with lower Apgar scores at 5 minutes, and exposed to meconium, sepsis, or surgery all had an increased likelihood of AKI. Conversely, multiple gestation, vasopressor exposure, antimicrobial exposure, and treatment with methylxanthines were all associated with a decreased risk of AKI. Although it seems counterintuitive that antimicrobial exposure was found to be associated with reduced risk for AKI, it can likely be explained because most neonates received short courses of treatment and were not septic. It is likely that this finding is confounded by indication, or in this case, the lack of indication. Treatment with methylxanthine is a fascinating observation and needs further exploration. Of 689 neonates of 32 weeks' gestation and less, 460 received a methylxanthine and 229 did not. The incidence of AKI in these 2 cohorts was 11.5% and 31.4%, respectively. That caffeine may be protective can be justified physiologically, but currently this remains only an association.

The determination of fluid balance in neonates presents several challenges. Although in adult and pediatric populations there is evidence that fluid overload is associated with increased mortality and morbidity, this is very difficult to study in newborns because complete and accurate ascertainment of intake and output is nearly impossible. Therefore, a change in weight compared with birthweight was used as a surrogate for fluid balance. Because both the admission diagnoses and the underlying physiology of term and preterm neonates are quite different, the AWAKEN population was divided into 2 cohorts for these analyses: infants at least 35 weeks' gestation at birth and infants less than 35 weeks' gestation. In the older cohort, there was a clear association between fluid balance and outcome, with infants whose weights increased by more than 10% during the first postnatal week having an increased need for mechanical ventilation at 7 days of age and those with the most negative fluid balance more likely to survive to discharge from the NICU.

One of the major limitations of AWAKEN was that it was a retrospective record review, and the collection of data was according to the local standard of care. Herein lies another of the important issues related to nAKI. The AWAKEN study has begun to identify the highest-risk populations, but the current laboratory studies may not be sensitive enough to detect early kidney injury. Creatinine increases only after considerable injury has already occurred. We need other biomarkers that can identify injury of a lesser degree so that efforts can be made to modify our care and minimize further injury. There are some candidate urinary biomarkers, but more work needs to be done to determine the most sensitive and cost-effective means of detection.

As neonatologists become more aware of the potential implications of AKI in the NICU population, practice guidelines for both early identification and amelioration of injury are needed. Appropriate surveillance paradigms, treatment regimens, and follow-up recommendations should be the goal of collaborations between neonatologists and pediatric nephrologists to improve the long-term outcomes and renal health of vulnerable neonates.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know how to interpret various renal function tests (eg, urinalysis, creatinine clearance).
- Know the clinical manifestations, imaging, and laboratory features of renal failure in the neonate.

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1. A male infant born at 28 weeks' gestational age is now 2 weeks old and weighs 1,150 g. He has abdominal distention and increasing cardiovascular instability and is diagnosed as having necrotizing enterocolitis. He is given nothing by mouth and placed on intravenous nutrition at 120 mL/kg per day. You are called to his bedside the next day to evaluate decreased urine output to 5 mL over the past 12 hours. His laboratory findings are significant for a blood urea nitrogen level of 26 mg/dL (9.3 mmol/L) and a serum creatinine level of 1.2 mg/dL (106.1 μmol/L) (compared with 12 mg/dL [4.3 mmol/L] and 0.7 mg/dL [61.9 μmol/L], respectively, the previous day). You suspect neonatal acute kidney injury (nAKI). Using the Kidney Disease: Improving Global Outcomes (KDIGO) classification system, what stage of nAKI does this infant have?
    - A. Stage 0.
    - B. Stage 1.
    - C. Stage 2.
    - D. Stage 3.
    - E. The stage of AKI cannot be determined with the information presented.
2. An infant born at 28 weeks' gestation with necrotizing enterocolitis is suspected of having nAKI. Preterm infants' susceptibility to nAKI is related to the typical course of renal development and nephrogenesis. Which of the following statements regarding renal development is CORRECT?
    - A. Nephron development begins at approximately 7 weeks' gestation and is complete at approximately 39 weeks' gestation.
    - B. Preterm birth halts glomerulogenesis.
    - C. Growth restriction is a key element of renal development, with nearly 200,000 additional nephrons for each increase of 500 g in birthweight.
    - D. The kidney continues a maturational process for nearly 5 years, at which time adult glomerular filtration rate is established.
    - E. Up to 60% of nephron development occurs during the third trimester.
3. In utero and NICU exposures have the potential to adversely impact renal development. Which of the following exposures predisposes to decreased ureteric bud branching?
    - A. Tobacco exposure.
    - B. Aminoglycoside exposure.
    - C. Corticosteroid exposure.
    - D. Vitamin D deficiency.
    - E. Protein restriction.
4. According to the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) retrospective cohort study, the presence of AKI has a significant effect on morbidity and mortality in neonates. Which of the following statements regarding infants with AKI is CORRECT?
    - A. They are 4 times more likely to die.
    - B. Their length of stay in the NICU increases by an average of 3 days.
    - C. They have a 30% increased risk of hospital readmission in the first month after discharge.
    - D. They have an increased need for packed red blood cell transfusions in the NICU, approximately a 10-fold likelihood.
    - E. They are at increased risk for threshold retinopathy of prematurity requiring laser surgery.

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5. Infants with a history of nAKI are at increased risk for chronic kidney disease (CKD) later in life. CKD stages are defined by glomerular filtration rate, most commonly estimated by serum creatinine concentrations. What other metric can be used to evaluate renal dysfunction in these patients?
   - A. Large kidney size secondary to glomerular hypertrophy.
   - B. Decreased serum cystatin C levels.
   - C. Impaired linear growth crossing at least 2 percentile lines.
   - D. Sustained blood pressure of at least the 95th percentile.
   - E. Decreased urinary angiotensinogen levels.

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Diagnosis and Management of Urinary Tract Infections in Premature and Term Infants

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Education Gaps

1. Data on the criteria for diagnosis and management of urinary tract infections in neonates are limited.
2. The indications for urologic imaging and prophylaxis in neonates are unclear.

Abstract

Urinary tract infections (UTIs) contribute to a significant portion of bacterial infections in neonates and young infants. Criteria for the diagnosis, treatment, and imaging are more established in the 2- to 24-month-old age group. It may not be ideal to apply recommendations from the group older than 2 months to younger patients, because the presentation, risk factors, complications, management, and imaging may not be appropriate for this more vulnerable population. This review provides a summary of the available literature for diagnosis, treatment, and follow-up of a UTI in the neonate or young infant. We review data on imaging to assess for underlying congenital anomalies of the urinary tract. We also provide insight on the use of antibiotic prophylaxis, particularly when vesicoureteral reflux is identified.

Objectives After completing this article, readers should be able to:

1. Review the most common organisms and risk factors for urinary tract infections (UTIs) in the neonatal population.
2. Describe the criteria for diagnosis of UTIs and the appropriate scenario to assess for concurrent infections.
3. Review the management recommendations for neonatal and infant populations.
4. Review current recommendations for imaging and follow-up in infants after their first UTI.
5. Review indications for prophylactic antibiotic therapy after UTIs in early infancy.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
CAP	continuous antibiotic prophylaxis
CFU	colony-forming unit
HPF	high-power field
RBUS	renal bladder ultrasonography
SPA	suprapubic aspiration
UA	urinalysis
UTI	urinary tract infection
VCUG	voiding cystourethrography
VUR	vesicoureteral reflux
WBC	white blood cell

BACKGROUND

Urinary tract infections (UTIs) are the most common bacterial infection in febrile newborns. (1) Studies focused on febrile infants likely underestimate the true prevalence of UTIs in infants because most infants do not present with fever, especially in the neonatal period. (2) Estimated prevalence in infants younger than 2 to 3 months ranges from 4.6% to 13.6%. (3)(4)(5)(6)(7) The reported prevalence in children younger than 24 months is estimated between 7% and 15.4%. (4)(5)(6)

Previously, it was thought that UTIs may be a "sentinel event for an underlying renal anomaly." The quoted incidence of congenital anomalies of the kidney and urinary tract is 0.3 to 1.6 per 1,000 live births. (8) Most studies in children aged 2 to 24 months found that 12% to 30% had renal ultrasonography anomalies, primarily vesicoureteral reflux (VUR), during an evaluation after their first UTI. (9)(10) A few studies that specifically focused on infants in the NICU showed a much smaller incidence of anomalies (3%), perhaps suggesting that in the younger population, the likelihood of congenital anomalies is much smaller, and affected infants may require a more limited evaluation. (11) This review will concentrate primarily on neonatal UTIs in patients without a congenital anomaly, and provide recommendations for an appropriate evaluation to rule out such anomalies.

EPIDEMIOLOGY

Escherichia coli continues to be the most common causative organism for neonatal UTIs, representing up to 80% to 88% of cases (Table 1). (4)(6)(9)(12)(13) *Enterobacter* species and *Klebsiella pneumonia* follow closely behind. Less common pathogens include *Pseudomonas aeruginosa, Enterococcus* species, group B *Streptococcus, Staphylococcus aureus, Citrobacter freundii, Serratia marcescens,* and *Klebsiella oxytoca*. Fungal pathogens, mainly *Candida* species, are predominantly nosocomial in origin. (14) Boys with VUR are more likely to present with the less common pathogens. (4)(9) In the neonatal population, gram-positive pathogens (*Enterococcus faecalis, S aureus,* group B *Streptococcus, Streptococcus pneumoniae)* are rare. Of note, in infants presenting with *E coli* sepsis, galactosemia should be included in the differential diagnosis. (15)

There is a strong male predominance of UTIs in the neonatal and infant population (<3 months of age), which differs significantly from older infants and children. (3)(6)(9) In a prospective multicenter trial of 1,000 febrile infants younger than 60 days, the absence of circumcision increased the risk of UTI by almost 10-fold in boys: 21% in uncircumcised boys versus 2% for circumcised boys versus 5% in girls. (4) These findings are supported by a meta-analysis of a similar patient population and a population-based study in northern California that found that circumcision markedly lowered medical costs and hospital admissions, especially in the first 3 months of age. (5)(16)

White race and ill appearance were previously thought to be risk factors for UTI, but correlation with race has been called into question in more recent studies. (4)(5)(17) Although VUR remains the most common anomaly and has been associated with as many as 20% of neonatal UTIs,

TABLE 1. **Frequencies of Urinary Tract Infection Pathogens in Infant Studies**

REFERENCE	ZORC ET AL, 2005 (4)	ISMAILI ET AL, 2011 (6)	BONADIO AND MAIDA, 2014 (9)	GREENHOW ET AL, 2014 (13)
Age of patients	≤60 days (febrile)	0–3 months	≤ 30 days (febrile)	1 week–3 months
No. of urine cultures	1,025	46	670	823
Organisms				
Escherichia coli	80%	88%	71%	60%
Klebsiella spp	9%	7%	10%	2%
Enterobacter spp	5%	2%	3%	0%
Enterococcus	–	–	10%	2%
Citrobacter spp	4%	–	–	–
Pseudomonas spp	1%	–	1%	–
Other (gram-positive organisms, fungal, etc)	–	2%	5%	26%

there appears to be no difference in risk of UTI based on sex, birthweight, gestational age, or mode of delivery. (9)(18) In contrast, in a study of infants younger than 2 months in a single NICU, the rate of anomalies in patients with a UTI was less than 5%, with the youngest patients and those with *Klebsiella* as a pathogenic organism more likely to have VUR. (9)(18)

Maternal history may also play a role in the risk of neonatal UTI, because maternal history of UTI, premature rupture of membranes, and maternal exposure to antibiotics may all increase the risk for UTI in neonates. (19) Although breastfeeding may be protective for infants against respiratory and gastrointestinal infections, it has not been found to be protective against UTIs in the first 3 months of age. (20) Some studies suggest that vitamin D administration may increase the risk for UTIs in neonates. (20) A summary of predisposing factors for UTIs in infants is provided in Table 2.

The American Academy of Pediatrics (AAP) published guidelines in 2011 (updated in 2016) for febrile infants aged 2 to 24 months with recommended stratifications for UTI evaluation compared with clinical follow-up based on risk of UTI. (10) Low-risk febrile infants could be monitored clinically without testing for UTI while higher-risk infants should have a urine culture or urinalysis (UA) followed by urine culture if abnormal. Neonates, especially premature neonates, are likely at higher risk for UTI and urosepsis based on multiple factors. Increased susceptibility, prolonged hospitalization, multiple interventions, including intravascular catheters, and exposure to multiple antibiotic courses may contribute to a prevalence rate as high as 20% in premature and low-birthweight infants. (21) There are virtually no reports of UTIs in premature infants in the first 24 hours of age. (22) Data exist to suggest that bacterial colonization of the skin, particularly of the prepuce of uncircumcised boys, coupled with higher susceptibility to ascending infection likely contributes to the higher prevalence of UTIs in preterm versus term neonates (16). Hematogenous spread from invasive catheters or other sources appears to be less likely in preterm infants than previously thought. (23)

TABLE 2. **Predisposing Factors for Urinary Tract Infection in Infants**

NEONATAL OR INFANT CHARACTERISTICS
Male (< 3 months)
Uncircumcised
Prematurity
Renal and urinary tract malformation
High temperature (≥102.2°F [≥39°C])
MATERNAL CHARACTERISTICS
History of urinary tract infection
Premature rupture of membranes
Exposure to antibiotics

CLINICAL PRESENTATION

The clinical presentation in the neonate can often be difficult to differentiate from neonatal sepsis due to neurologic immaturity and nonspecific associated symptoms. (14) Poor feeding, lethargy, vomiting, diarrhea, irritability, feeding intolerance, hypothermia, hypoglycemia, abdominal distention, bradycardic events, and prolonged jaundice may all be presenting symptoms in a neonate with a UTI. Prolonged jaundice can be a presenting symptom in both term and preterm neonates. (2) Although the onset of jaundice after 8 days of age has a particular association with UTI, the AAP recommends screening for UTI in all infants with an elevated direct bilirubin concentration. (10) Fever with a high temperature (≥102.2°F [≥39°C]) is associated with a higher incidence of spontaneous bacterial infection compared with a viral illness. (4) However, up to half of infants with a UTI may only have a low-grade temperature or are afebrile, contributing to the difficulty in diagnosis and need for a high index of suspicion in neonates. (9)(21)

The risk of bacteremia associated with a UTI in infants is inversely related to age. One study showed a 5.7% correlation of a positive blood culture with a known UTI. (24) In a comparison of age-matched controls with bacteremic UTI versus nonbacteremic UTI, elevated serum band count (as a percentage of total white blood cell [WBC] count) and microscopic UA with more than 100 WBCs per high-power field (HPF) were more likely in the bacteremic UTI group. (24) In a 20-center retrospective review of older infants (aged 29-60 days) who presented to the emergency department with temperature greater than 100.4°F (38°C) and UTI, adverse events (death, shock, bacterial meningitis, ICU admission, etc) were found in 2.8% and bacteremia occurred in 6.5%. (25) A clinical prediction model identified a cohort at “low risk for adverse events” (not clinically ill and no medical history of high risk) with a peripheral band count of less than 1,250 cells/μL and absolute neutrophil count of greater than or equal to 1,500 cells/μL. (25) Of these low-risk patients, 28 of 862 (3.2%) were bacteremic and none had an adverse event. (25) While this model focused on an older and lower-risk cohort, it is possible that this could be true for low-risk preterm neonates as well. The risk of meningitis is low (0%–6%), (9) which could support potentially avoiding lumbar punctures in well-appearing neonates with a suspected or laboratory-proven UTI. (26)

DIAGNOSTIC CONFIRMATION

It is often difficult to collect urine in neonates. While suprapubic aspiration (SPA) and urethral catheterization are preferred methods because of the high contamination rates with sterile bag collection, the AAP recommendations for infants aged 2 to 24 months allow for sterile bag collection for an initial UA. If the UA findings are abnormal (positive leukocyte esterase or nitrite test or microscopic analysis results for leukoctyes or bacteria), a catheter or SPA sample should be sent for culture. (10) Applying this recommendation to a younger population may not be ideal, given the lack of reliability of UA in infants and the high false-positive rate of sterile bag collection. (10) Pyuria, defined as more than or equal to 5 WBCs/HPF, predicts less than 50% of infant UTIs. (27) Use of an enhanced UA (hemocytometer cell count and Gram stain on uncentrifuged urine specimens), which defines pyuria as greater than or equal to 10 WBC/μL, has 91% sensitivity and 96% specificity for positive urine cultures. (28) The use of an enhanced UA method with the low-risk criteria proposed by the AAP improves the identification of infants at lower risk for bacteremia; however, enhanced UA is not readily available in most laboratories at this time. (1)

The gold standard for diagnosis is a urine culture that is positive for a single organism. The threshold for a "positive" culture via SPA or sterile catheter collection varies in the literature between: 1) greater than or equal to 10,000 colony-forming units (CFUs) per milliliter of a single organism in addition to pyuria on enhanced UA, and 2) greater than or equal to 50,000 CFU/mL of a single organism (which the AAP recommends for 2- to 24-month-old neonates). (10)(17) While some studies postulate that 10,000 to 50,000 CFU/mL may represent asymptomatic bacteriuria, (17)(28) increasing this threshold to greater than or equal to 100,000 CFU/mL, even for a bag specimen, may have a 7.5% to 20% false-positive rate. (17)(29) Most experts suggest a threshold of greater than or equal to 50,000 CFU/mL of a single organism via SPA or sterile catheterization to make the diagnosis, and incorporating enhanced UA or clinical symptoms may help confirm a diagnosis of UTI. (10)(17) For lower colony counts on a urine culture in a neonate (10,000–50,000 CFU/mL), the authors suggest the following: if more than or equal to 10,000 CFU/mL of any organism(s) is grown on a suprapubic aspirate or a single organism grows on a catheterized specimen, and there are other clinical indicators of infection, concern for a true UTI should be raised. Bagged specimens are discouraged and should not be used for culture because of their high false-positive rates. A bagged specimen sent for culture that returns negative, however, can be reassuring.

Other laboratory findings, such as an elevated C-reactive protein or erythrocyte sedimentation rate, have low sensitivity and specificity. However, a positive urine culture via SPA (>100 CFU/mL) in combination with pyuria on enhanced UA (≥10 WBC/μL), a C-reactive protein level higher than 20 mg/L (190 nmol/L), or an erythrocyte sedimentation rate higher than 30 mm/hour was found to have a specificity of 98% and 97%, respectively, in a population of 162 febrile infants younger than 8 weeks. (3) Serum leukocytosis and positive leukocyte esterase or nitrite on urine dipstick may be helpful as supplemental tests, but are unreliable in the neonatal and infant population because of frequent bladder emptying. (9)(30)

MANAGEMENT

Initial management for a neonate with a UTI is inpatient intravenous broad-spectrum antibiotics—ampicillin and gentamicin or ampicillin and cefotaxime—followed by narrowing the regimen based on organism sensitivity. (6)(12) In the United States, ampicillin resistance in neonatal *E coli* isolates has been reported in up to 75%, with gentamicin resistance reported to be between 12% and 17%. (31) Despite this high resistance to ampicillin, there is a reported 50% clinical response in patients, suggesting discordance between in vitro and in vivo activity or high concentration in the urine. (32) The current diagnostic approach and management for a neonate with a UTI is summarized in the Fig.

Data on outpatient and/or oral treatment are based mostly on older infants, so safety in this younger age group is not yet known. (6) For febrile infants aged 2 to 24 months, the AAP recommends either intravenous or oral antibiotics for 7 to 14 days based on local sensitivity. (10) Empirical treatment is thought to be important because of the high risk for bacteremia in the newborn period associated with UTIs and to prevent renal scarring. However, some more recent studies have shown no statistical difference, but rather a trend toward long-term scarring with oral versus initial intravenous antibiotics followed by oral antibiotics. Non-*E coli* uropathogens appear to be more likely to result in renal scarring. (33) Duration of treatment for infants less than or equal to 60 days of age varies between less than or equal to 4 days and 7 to 14 days, though the majority are treated intravenously for 5 to 7 days. (24)

For treatment of infants younger than 60 days who have a bacteremic UTI, retrospective review of multiple institutions revealed a mean duration of intravenous antibiotics of 6.3 to

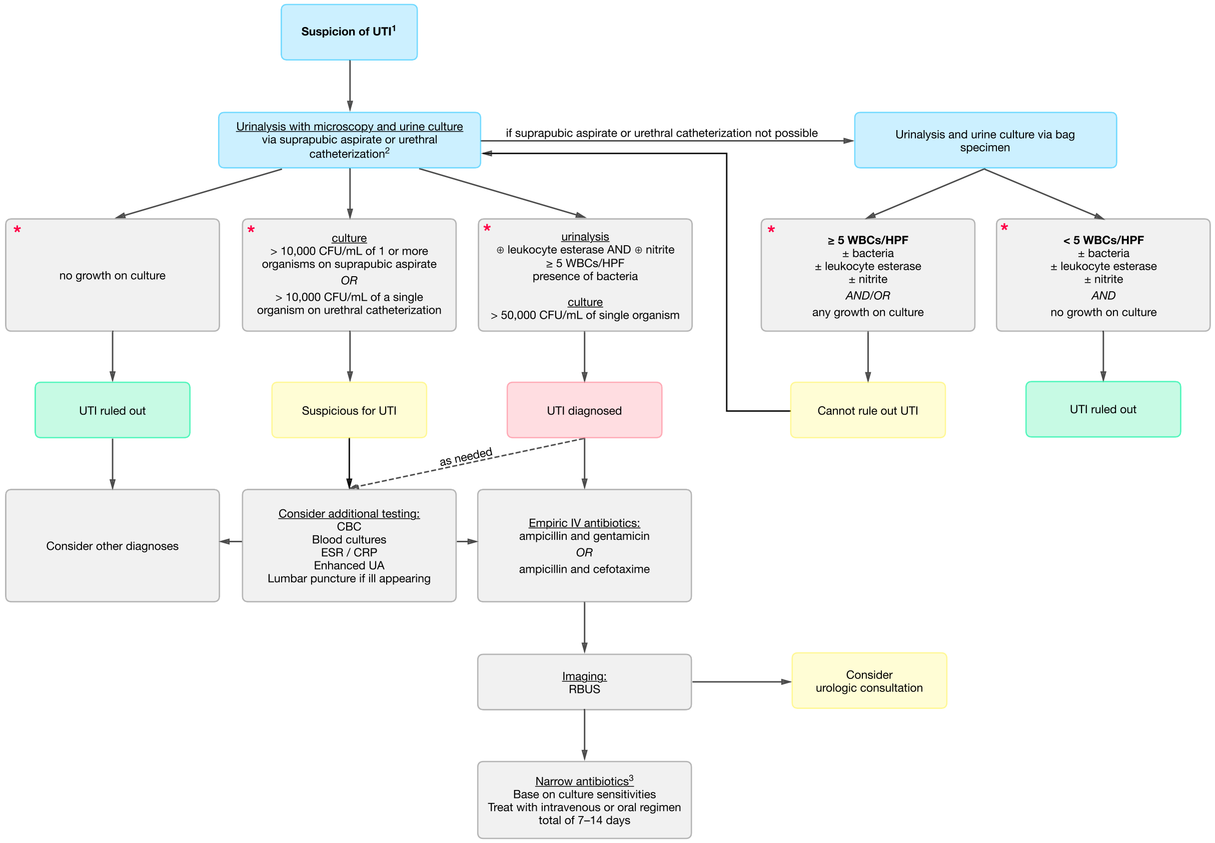
Suspicion of UTI^1
Urinalysis with microscopy and urine culture via suprapubic aspirate or urethral catheterization^2
if suprapubic aspirate or urethral catheterization not possible
Urinalysis and urine culture via bag specimen
*
no growth on culture
*
culture
> 10,000 CFU/mL of 1 or more organisms on suprapubic aspirate
OR
> 10,000 CFU/mL of a single organism on urethral catheterization
*
urinalysis
⊕ leukocyte esterase AND ⊕ nitrite
≥ 5 WBCs/HPF
presence of bacteria
culture
> 50,000 CFU/mL of single organism
*
≥ 5 WBCs/HPF
± bacteria
± leukocyte esterase
± nitrite
AND/OR
any growth on culture
*
< 5 WBCs/HPF
± bacteria
± leukocyte esterase
± nitrite
AND
no growth on culture
UTI ruled out
Suspicious for UTI
UTI diagnosed
Cannot rule out UTI
UTI ruled out
as needed
Consider other diagnoses
Consider additional testing:
CBC
Blood cultures
ESR / CRP
Enhanced UA
Lumbar puncture if ill appearing
Empiric IV antibiotics:
ampicillin and gentamicin
OR
ampicillin and cefotaxime
Imaging:
RBUS
Consider urologic consultation
Narrow antibiotics^3
Base on culture sensitivities
Treat with intravenous or oral regimen
total of 7–14 days

Figure. Flow chart of diagnostic workup for neonate with suspicion for UTI. 1, Clinical signs of illness are fever, hypothermia, lethargy, irritability, feeding intolerance, apneic or bradycardic events, prolonged jaundice, etc. 2, Suprapubic aspiration of bladder or urethral catheterization are preferred method of obtaining urine sample for testing. Bag collection of urine is useful to rule out UTI if testing is negative. 3, Antibiotic course may vary depending on age and severity of illness; may consider transition to oral antibiotics if >3 months of age and otherwise normal laboratory findings and negative cultures. *Interpretation of urinalysis with microscopy and urine culture can be challenging in the context of conflicting information (which is very common). Index of suspicion should go up with congruent, positive findings and similarly, index of suspicion should decrease with incongruent findings.

7.8 days ± 4 days with few relapses. (34) Fever resolves in most patients within 12 to 24 hours. (12) Transition to oral antibiotics after initial intravenous broad-spectrum coverage may be considered in older infants (>3 months) if clinically well with otherwise normal laboratory findings and negative blood or cerebral spinal fluid cultures, because there appears to be no difference in risk for renal scarring. (35) However, the bioavailability, safety, and efficacy of oral antibiotics are unknown in premature infants, so completion of an intravenous course of antibiotics is preferred. Neonates are typically treated for 10 to 14 days, but the gaps in understanding the treatment course with outcomes remain.

MANAGEMENT OF RECURRENT UTIs AND ANTIBIOTIC PROPHYLAXIS

Recurrent UTIs

The treatment and prevention of recurrent UTIs can be challenging and require close coordination among the family, clinical team, and consulting services. The approach is tailored for each individual patient and any identified factors (eg, male, uncircumcised, premature birth, presence of congenital anomalies, prior UTI, clinical circumstances regarding past infection, height of fever). There is no consensus about the definition of recurrent UTIs. However, the treating or consulting physician should be wary of labeling patients with this diagnosis in the absence of strong evidence. In particular, multiple positive urine cultures separated by time and completed treatment represent a bare minimum for UTI to be considered recurrent. The authors do not advise repeating urine cultures during or after treatment of a UTI unless there is clinical suspicion (eg, fever, lethargy, poor oral intake) for recurrence of infection, incomplete treatment, or symptoms. In some circumstances, if a urine culture is repeated, the presence of an ongoing UTI may signify incomplete treatment or newly acquired antibacterial resistance to treatment.

In boys with recurrent UTIs, strong consideration for circumcision should be discussed with the family, particularly in patients younger than 6 months. (36) Uncircumcised boys have at least 50% higher incidence of UTI than circumcised boys, and circumcision alone can reduce future UTI incidence. (16) There is no strict threshold for which circumcision is offered with regard to recurrent infections. Cultural, religious, and social considerations may weigh on the decision to proceed with circumcision, in addition to other factors such as placement on daily prophylactic antibiotics and the presence of other uncorrected, congenital urologic abnormalities.

Renal bladder ultrasonography (RBUS) is recommended after a diagnosis of a UTI in an infant to rule out new or worsening urinary tract dilation, urolithiasis, or abscess (rare). (37) Repeat RBUS for patients with previous imaging studies should also be strongly considered. As noted earlier, although the risk for concomitant identification of a congenital urologic abnormality is fairly low among neonates with a UTI and even fewer require intervention, the presence of these anomalies can inform future risk and help direct further therapy. Congenital anomalies with a predisposition to urinary stasis or obstruction (eg, posterior urethral valves, ureteropelvic junction obstruction, congenital megaureter, neurogenic bladder) may require surgical intervention to reduce the risk of future infections. As such, urologic consultation is important.

Continuous Antibiotic Prophylaxis

Continuous antibiotic prophylaxis (CAP) is an important component of UTI prevention in patients with congenital anomalies such as VUR, because such prophylaxis has been found to lead to a 50% reduction in future UTIs. (38)(39) Evidence for CAP in the setting of UTI and VUR is generalized from large, randomized controlled trials such as the Swedish Reflux Trial (40) and the RIVUR Study, (39) which showed clear benefits of CAP in the prevention of UTI. The data are generalized to the neonate population because the Swedish Reflux Trial did not include patients younger than 1 year and the RIVUR Study did not include infants younger than 2 months. (39)(40) Support for the broad use of CAP for various congenital anomalies in neonates is of low quality, with better evidence in specific conditions (eg, high-grade hydronephrosis, VUR). (41)

The American Urological Association guidelines do not specifically address the circumstances of premature infants and neonates, but do recommend that patients with a febrile UTI and any grade VUR be placed on CAP. (36) Other clinical and diagnostic circumstances may also warrant CAP in this age group, given their risk for sequelae from UTI (sepsis, bacteremia). In neonates, amoxicillin is typically used for CAP. Alternatives include orally available cephalosporins (eg, cephalexin). Trimethoprim-sulfamethoxazole is avoided in the first 2 months of age in neonates because of the risk of kernicterus. Nitrofurantoin is also avoided in the first month of age because of the risk of hemolytic anemia, particularly in infants with glucose-6-phosphate dehydrogenase deficiency. The authors recommend that if CAP is considered appropriate for a patient, the intended drug of choice should ideally fall within the sensitivities found on any previous cultures of organisms. Use of oral antibiotics that have been approved by the US Food and Drug Administration (FDA) are limited in this population, and this approach may not be possible in patients with a history of drug-resistant organisms. Table 3 provides a summary of common medications used for CAP, dosage, FDA-approved ages and indications, and common adverse effects.

Imaging

While specific guidelines are not available to guide imaging options before age 2 months, some experts have argued that any UTI should be considered pathologic in this age group. Given the potential for recurrent UTIs or sequelae from a UTI in patients with congenital anomalies, imaging is recommended for all neonates diagnosed with an organism-confirmed UTI. The prevalence of congenital urinary tract anomalies in preterm infants and neonates younger than 2 months hospitalized for a UTI remains high, with 35% to 40% having a finding on RBUS. (6)(11) In most cases, mild hydronephrosis is noted. Only 5% of all patients demonstrated more severe pathologies (eg, high-grade hydronephrosis, horseshoe kidney, unilateral renal agenesis, congenital megaureter).

The usefulness of imaging after a diagnosis of a UTI in an infant is predicated on the accuracy of the diagnosis. To minimize cost, false-positive rates, and unnecessary diagnosis of benign phenotypes, the AAP recommends that patients with a UTI at 2 to 24 months of age have imaging only if they develop a second febrile UTI. Because a large proportion of patients who have a UTI at age 2 to 24 months will not develop another, this strategy minimizes overuse of imaging (and subsequent imaging and procedures that tend to follow). However, this strategy may not be appropriate for premature infants and neonates younger than 2 months, but the practitioner should still be wary of overuse and disadvantages of imaging in neonates. To this end, accurate diagnosis of UTI is paramount, and we recommend that clinical suspicion for a UTI be gauged on the strength of the underlying evidence. For example, a bagged urine specimen is considered inadequate for the diagnosis of UTI, because it is associated with a high false-positive rate. A single organism growing 50,000 CFU/mL from an SPA, however, would serve as definitive proof for a UTI in a sick patient.

Ultrasonography is the mainstay of urinary tract imaging in infants and children. Ultrasonography is noninvasive and

TABLE 3. **Common Medications Used for CAP**

MEDICATION	TREATMENT DOSE	CAP DOSE	FDA-APPROVED INDICATIONS	COMMON ADVERSE EFFECTS
Amoxicillin	25–45 mg/kg per day PO divided into 2 doses	15–20 mg/kg daily	Any age, UTI treatment	Cutaneous/allergic reactions, gastrointestinal disturbances
Cephalexin	25–50 mg/kg per day PO divided into 2–4 doses	25 mg/kg daily or divided into 1–2 doses	Any age, UTI treatment	Cutaneous/allergic reactions, gastrointestinal disturbances
Nitrofurantoin	5–7 mg/kg daily divided into 4 doses	1–2 mg/kg daily	>1 month age, UTI treatment or prophylaxis	Hemolytic anemia, gastrointestinal disturbances, interstitial pneumonitis, cutaneous/allergic reactions
TMP	8–10 mg/kg TMP daily divided into 2 doses	2 mg/kg TMP daily	>12 years age, UTI treatment or prophylaxis	Cutaneous/allergic reactions, hematologic toxicity
TMP-sulfamethoxazole	8–10 mg/kg TMP daily divided into 2 doses	2 mg/kg TMP daily	>2 months age, UTI treatment or prophylaxis	Cutaneous/allergic reactions, hematologic toxicity, hepatotoxicity (kernicterus)

CAP=continuous antibiotic prophylaxix; FDA=Food and Drug Administration; PO=orally; TMP=trimethoprim; UTI=urinary tract infection.

avoids ionizing radiation, while providing detailed imaging of the urinary tract. The technique is operator-dependent. Its use in older infants and children with a first UTI has been debated in the past, and current AAP recommendations state that ultrasonography should be performed only after a second UTI. This recommendation is based on studies showing lack of cost-effectiveness and that a majority of older patients (2–24 months) do not have a second UTI or sequelae. (10) Such guidelines have not been established for premature infants or neonates younger than 2 months.

Possible imaging findings that should prompt urologic consultation include:

- Presence of hydronephrosis or hydroureteronephrosis (also referred to varyingly as "pelviectasis" or "calyectasis" by some radiologists)
- A duplex collecting system
- Ureterocele
- Megaureter (dilated, tortuous ureter distally with or without dilation of the collecting system and pelvis at the kidney)
- Posterior urethral valves (dilated posterior urethra as seen on sagittal views of the bladder)
- Renal cysts
- Multicystic dysplastic kidney
- Bladder diverticulum
- Urolithiasis

Newer ultrasound techniques offer the ability to visualize the presence of VUR and even grade it, though this technique is not widely available.

Voiding cystourethrography (VCUG) remains the test of choice for diagnosing VUR and ruling out some other congenital anomalies. A normal finding on RBUS does not necessarily rule out the presence of VUR. (6)(42) Some centers advocate that a VCUG be performed only in the setting of an abnormal RBUS finding, non–*E coli* UTI, or recurrent UTI. We advocate for testing of all premature infants with a UTI, because these patients have an increased likelihood of immature urinary tracts and thus, may be more susceptible to the risks of upper tract infection (see section on sequelae) without proper identification and treatment. (43) One recent study of patients with a UTI at less than 3 months of age noted that the risk of identification of a high-grade VUR was greatest in patients with non–*E coli* UTI and abnormal ultrasound findings (55% with high-grade VUR).

In patients with normal ultrasound findings and non–*E coli* UTI, the risk of identification of high-grade VUR decreased to 26%. (44)

A VCUG should only be performed after treatment of UTI has been completed. (45) If there is a strong suspicion for VUR, the patient may be started on antibiotic prophylaxis after completion of treatment-dose antibiotics to minimize the risk of recurrent UTIs. During a VCUG, a urethral catheter is placed in the bladder, contrast is then instilled into the catheter, and multiple radiographs are obtained of the bladder and urethra. Images are taken of the renal fossae to look for the presence of contrast medium in the upper urinary tracts. Characteristics examined include presence or absence of VUR, associated timing (early, late, voiding), and grade (scale of 1 to 5, with 1 indicating reflux limited to the ureter and 5, severe dilation of the ureters, renal pelvis, and calyces); bladder contour regularity; presence/absence of bladder diverticulae and bladder neck; and posterior urethra configuration (specifically to assess for posterior urethral valves, which would show a dilated posterior urethra, filling defect, and bladder neck with hypertrophy).

Other Imaging Modalities

Magnetic resonance urography and nuclear function testing (Tc-99m mercaptoacetyltriglycine [Mag3], diethylenetriaminepentacetate, or dimercaptosuccinic acid) are not routinely recommended for evaluation of an infant with an isolated UTI. These adjunct, specialized imaging tests may be ordered by consulting services to identify or rule out specific urinary tract abnormalities. Magnetic resonance urography uses nonionizing radiation, but nuclear function testing requires radiation. Nuclear function testing is advocated by some experts to address potential reflux as an initial screen before VCUG ("top-down approach"), but this approach is not widely practiced in North America owing to the lack of availability of the radioactive tracers. (46) Computed tomography is not routinely used to evaluate the urinary tract in neonates or infants, owing to better nonionizing alternatives.

SEQUELAE

Sequelae of UTIs in neonates must be considered, particularly in those with risk factors: prematurity, presence of antenatal hydronephrosis, presence of known congenital urinary tract anomaly such as VUR, non–*E Coli* pathogen, drug-resistant organisms, or recurrent UTIs. Immediate sequelae of a UTI in this population include bacteremia in up to one-third of patients, though more recent studies show that this association may be closer to 5% of patients. (24)(47) Renal growth rates have been shown to be slower in a small cohort (n=22) of patients younger than 1 month with a UTI. Long-term follow-up (mean age, 17 years) showed renal size normalized, but there was size disparity in patients with VUR. (48)

The subsequent development of renal scarring, chronic kidney disease, and hypertension are also of concern in patients with a UTI at an early age. Delay in initiation of treatment for a febrile UTI has been shown in some studies to increase the risk of renal scarring, even in patients without VUR. (49)(50)

There has long been felt to be a strong relationship among UTI, VUR, and the development of renal scarring, which occurs in about 10% of patients with UTI and VUR. (39) However, recently it has been increasingly recognized that VUR and renal dysplasia exist on the same spectrum, and dysplastic kidneys are more likely to harbor or be susceptible to renal scarring. Similarly, such kidneys may already be at risk for poor growth and atrophy, further confounding long-term outcome measures in this patient population, and making it difficult to attribute these outcomes solely to a UTI or other predisposing conditions. (33)(43) Overall, risk of chronic kidney disease or hypertension after a UTI in the neonatal period appears to be low.

CONCLUSION

The estimated prevalence of a UTI in infants younger than 3 months is 4.6% to 13.6% based on limited data. Neonates and young infants often present with nonspecific symptoms that make diagnosis difficult and require a high index of suspicion. The most common pathogen in neonatal UTIs is *E coli*, but the risk factors differ for neonates versus older children. Significant risk factors include male gender, lack of circumcision, prematurity, renal and urinary tract malformation, maternal exposure to antibiotics, and maternal UTI. Suprapubic aspirate, or more often a sterile catheter specimen, is preferred for diagnosis and culture of a single organism, with greater than or equal to 50,000 CFU/mL being the most commonly accepted threshold. However, lower colony counts of a single organism in the setting of strong clinical indicators may also be consistent with a UTI. Pyuria on UA and supplemental testing may help make the initial diagnosis. Bacteremia and meningitis are rare in this population but still represent a significant risk if missed. Empirical treatment with intravenous broad-spectrum antibiotics is preferred, with narrowing based on sensitivities. A 10- to 14-day intravenous course of antibiotics is typical for neonates, though evidence shows that transition to oral antibiotics may be possible. Imaging with RBUS should be considered for all patients in this age group, with further imaging predicated on patient risk factors. Antibiotic prophylaxis has been shown to be beneficial in preventing recurrent UTIs in patients with VUR, but may be considered in infants with less common congenital urinary tract anomalies in consultation with a specialist.

PARENT RESOURCES

- Preventing urinary tract infections in children: https://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Prevent-Urinary-Tract-Infections-in-Children.aspx
- Circumcision: https://www.healthychildren.org/English/ages-stages/prenatal/decisions-to-make/Pages/Circumcision.aspx
- Detecting urinary tract infections: https://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Detecting-Urinary-Tract-Infections.aspx

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causative infectious agents, pathogenesis, and differential diagnosis of urinary tract infections.
- Know the clinical and laboratory features, treatment, and complications of urinary tract infections.

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NeoReviews Quiz

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1. A 2-month old infant presents with fussiness, poor feeding, and fever. Diagnostic evaluation is suspicious for urinary tract infection. Which of the following statements regarding newborns and urinary tract infections is correct?
   - A. Urinary tract infections represent the most common bacterial infection in febrile newborns.
   - B. Most infants with urinary tract infections present with fever.
   - C. Younger neonates with urinary tract infection (<1 week old) are more likely to have fever than older infants (>2–3 months) with urinary tract infection.
   - D. Urinary tract infections in infants younger than 2 months are exceedingly rare, with prevalence of 1 per 1,000 live births.
   - E. Urinary tract infection in a 2-month-old signifies a greater than 50% likelihood of renal anomaly.
2. A 3-week-old male infant is found to have urinary tract infection after presenting with poor feeding, emesis, and intermittent fever. A urine culture is noted to be growing bacteria. Which of the following is the most common causative organism for urinary tract infection in the neonatal period?
   - A. *Enterobacter* species.
   - B. *Klebsiella* pneumonia.
   - C. *Escherichia coli.*
   - D. *Pseudomonas aeruginosa.*
   - E. *Staphylococcus aureus.*
3. A 1-month-old infant is being evaluated for fever and lethargy. The urinalysis findings are suspicious for urinary tract infection. Which of the following increases the risk for urinary tract infection by approximately 10-fold?
   - A. Absence of circumcision.
   - B. Being female compared with male.
   - C. White race compared with any other race.
   - D. Cesarean delivery.
   - E. Placement of gastric suction catheter during delivery resuscitation.
4. An 8-day-old infant presents with jaundice and irritability. Serum direct bilirubin level is elevated. Which of the following statements regarding presentation of urinary tract infection in neonates is correct?
   - A. Neonates with urinary tract infections almost always (>90% of the time) present with 1 of the following: temperature greater than 101.3°F (38.5°C) or hypothermia with temperature less than 95°F (35°C).
   - B. The risk of bacteremia associated with urinary tract infection in infants is directly and linearly correlated with increasing age.
   - C. The most common presenting sign of urinary tract infection is hyperglycemia.
   - D. Prolonged jaundice can be a presenting symptom in both term and preterm neonates.
   - E. Although jaundice can be a symptom of urinary tract infection, testing for urinary tract infection should only be performed for indirect hyperbilirubinemia that presents after 2 weeks of age.

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5. A 3-month-old infant presents to the emergency department with low-grade fever, feeding intolerance, and increasing lethargy. Which of the following statements regarding testing for urinary tract infection in this patient is correct?

   A. The initial urinalysis should be performed by using a capillary tube on a wet diaper.
   B. Suprapubic aspiration should be performed on each of the 4 quadrants of the bladder.
   C. A urine culture growing more than 50,000 colony-forming units per milliliter of a single organism would be considered as a confirmatory diagnosis of urinary tract infection.
   D. Bagged urine specimens are just as accurate as catheterized specimens in the neonatal period.
   E. Elevated C-reactive protein concentration is a highly sensitive and specific test for bacterial urinary tract infection in infants up to 6 months of age.

Diagnosis and Management of Urinary Tract Infections in Premature and Term Infants

Angela Lai, Kyle O. Rove, Sachin Amin, Gino J. Vricella and Douglas E. Coplen

NeoReviews 2018;19;e337
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1 Upper Gastrointestinal Hemorrhage in a Healthy Term Infant

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AUTHOR DISCLOSURE Drs Ahamed, Yu, Batton, and Nimavat have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant is born via spontaneous vaginal delivery at 40 weeks of gestation to a 34-year-old multigravida who has diet-controlled gestational diabetes. Meconium-stained amniotic fluid is noted with rupture of membranes 3 hours before delivery. The infant is vigorous after birth, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The neonate's birthweight is 4,050 g (98th percentile). The initial physical examination findings are normal and she is allowed to room in with her mother. Vitamin K is administered within 1 hour of birth.

Due to ineffective attempts at lactation, the neonate receives supplementation with term formula once during the first 24 hours. There is no documented void before 24 hours and a neonatology consultation is requested. During the physical examination in the newborn nursery, at 26 hours of age, she passes a large bloody stool with a significant amount of bright red blood. The infant appears well and nondistressed, with normal vital signs, good perfusion, and no respiratory distress. The abdomen is soft, nondistended, and nontender. No anal fissures are noted. Her examination findings are otherwise unremarkable. Review finds that she also had an episode of brownish emesis earlier in the day, which is attributed to swallowed maternal blood. The infant is transferred to the NICU.

An Apt-Downey test on the stool could not be performed because the sample was contaminated with meconium and red blood cells could not be eluted. Laboratory results are as follows: hemoglobin, 14.1 g/dL (141 g/L); hematocrit, 40.8%; platelet count, $244\times10^3/\mu L$ ($244\times10^9/L$); C-reactive protein, 3.4 mg/dL (32.3 nmol/L); prothrombin time, 16.6 seconds; and partial thromboplastin time, 31.6 seconds. An abdominal radiograph demonstrates a normal bowel gas pattern. A Replogle tube is placed and it drains blood-stained fluid. She is given nothing by mouth, started on intravenous fluids, and administered empirical antibiotics after obtaining a blood culture.

Over the next 8 hours, the infant continues to pass several large bloody stools with blood clots. Approximately 110 mL of blood-stained gastric fluid is drained from the stomach. The hemoglobin level decreases to 9.3 g/dL (93 g/L) during this time. However, she is not tachycardic and her blood pressure remains normal with normal peripheral perfusion. Between 24 and 48 hours of age, 40 mL/kg of crystalloid boluses and 40 mL/kg of packed red blood cells are administered because of the continuing drop in the hemoglobin level; pediatric surgery, gastroenterology, and hematology are consulted.

DISCUSSION

Diagnosis

Localizing the source and causes of gastrointestinal (GI) bleeding in a well-appearing term infant can be challenging. The most likely cause is swallowed maternal blood, which can be confirmed by performing an Apt-Downey test. Although results of this test were not available in this case, the decreasing hemoglobin level, bloody stool noted on gross examination, and bloody Replogle drainage strongly suggested a pathologic cause of upper GI tract bleeding. The differential diagnoses included bleeding due to hepatic failure, hematologic conditions, infection, necrotizing enterocolitis, hemorrhagic gastritis, esophagitis, gastric ulcer, Meckel diverticulum, an arteriovenous malformation (AVM), or other rare anomalies of the GI tract. Bleeding from a hepatobiliary source or due to a hematologic condition seemed unlikely because of the normal coagulation profile and platelet count and the absence of hepatosplenomegaly. Infections such as sepsis and necrotizing enterocolitis also seemed unlikely because the infant appeared to be well, there were few risk factors for infection, and radiographs of the chest and abdomen were unremarkable. Although uncommon in newborns, hemorrhagic gastritis was considered the most likely etiology in our infant based on the large amount of bleeding and her overall condition. An AVM, gastric ulcer, and Meckel diverticulum remained considerations.

Course

In consultation with the pediatric gastroenterologist, intravenous pantoprazole was started as presumptive treatment of hemorrhagic gastritis. Because the infant was hemodynamically stable and did not have any evidence of coagulopathy, invasive procedures such as exploratory laparotomy or upper GI endoscopy and further imaging studies to evaluate and treat other causes such as an AVM or Meckel diverticulum were deferred.

Once pantoprazole was initiated, within 12 hours, the volume of bloody gastric aspirate reduced and turned clear between 48 and 72 hours. Blood was no longer grossly visible in the stool and by postnatal day 5 the stools were no longer guaiac positive for blood. The Replogle tube was removed on postnatal day 4, and feeds were introduced and advanced uneventfully beginning on day 5. Intravenous pantoprazole was given for 5 days followed by oral dosing. She was discharged from the hospital on postnatal day 7 on oral pantoprazole. At 2 months of age, she had not had any recurrence of GI bleeding and had achieved good growth and development.

The Condition

Upper GI bleeding is defined as GI bleeding proximal to the ligament of Treitz. Approximately 20% of GI bleeding in children is from an upper GI source. Significant upper GI bleeding is uncommon in healthy term neonates. When it does occur, the most common presentation is hematemesis or bloody gastric aspirates, but bright red blood in the stools has also been reported due to the rapid intestinal transit in neonates.

In healthy-appearing term neonates, hematemesis or bloody gastric aspirates are almost always caused by swallowed maternal blood. This diagnosis can be made by performing an Apt-Downey test which detects the presence of fetal cells in either the gastric aspirate or stools. The most common pathologic causes of neonatal upper GI bleeding are esophagitis and gastritis. Most cases of esophagitis and gastritis are, however, asymptomatic, with only 6% to 12% of the children in intensive care presenting with significant lesions to cause any GI bleeding. These cases tend to present with blood-tinged emesis and usually resolve spontaneously. Significant upper GI bleeding associated with hypovolemia, shock, and death is usually related to perinatal stress, hypoxemia, respiratory failure, congenital heart disease, raised intracranial pressure, or infection. Additional rare causes that have been reported include coagulopathy due to liver dysfunction, portal venous thrombosis leading to an esophageal variceal bleed, hemorrhagic disease of the newborn due to vitamin K deficiency, intestinal duplication, or an AVM. Milk protein intolerance is usually associated with lower GI bleeding typically beyond 7 days of age, though it can sometimes present with esophagitis.

Gastric ulcers are rare among infants in the neonatal period. When they do occur, they are usually secondary to an underlying illness; however, the origin of stress-induced gastric lesions in infants is poorly understood. Few cases of massive upper GI bleeding due to hemorrhagic gastritis in otherwise healthy infants have been reported.

The mainstay in management for an infant with GI bleeding is restoring and maintaining hemodynamic stability. Crystalloid fluid boluses and blood transfusions should be administered judiciously and rapidly to ensure adequate perfusion. With the advent of smaller endoscopes, esophagogastroduodenoscopy may be considered to diagnose and treat the source of GI bleeding. This procedure is relatively safe, but potential therapeutic benefits may be limited by the small size of the scope required for a neonatal procedure. Use of an H2 blocker such as ranitidine has been shown to be beneficial in controlling mild to moderate upper GI bleeding within 24 to 48 hours with no recurrence of episodes of bleeding. In a case control study of infants who presented with upper GI bleeding, the mucosal lesions were noted to resolve in 75% of patients within 28 days of the use of H2 blockers. Data regarding the use of proton pump inhibitors in neonates are limited. Both of these classes of medications reduce gastric acid secretion and increase the pH of gastric contents. In rare instances, bleeding cannot be controlled with conservative management, and endoscopy or exploratory laparotomy may be required.

Lessons for the Clinician

- Upper GI bleeding in a healthy term infant can be a diagnostic challenge.
- When upper GI bleeding is not the result of swallowed maternal blood, extensive evaluation should be performed to identify the cause.
- If hemorrhagic gastritis is suspected and the neonate is hemodynamically stable without significant coagulopathy, a trial of an H2 blocker or proton pump inhibitor may be considered before proceeding with more invasive evaluation and treatment.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations and differential diagnosis of GI bleeding in newborn infants, including the various coagulation disorders that cause GI hemorrhage.

Suggested Readings

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Case 1: Upper Gastrointestinal Hemorrhage in a Healthy Term Infant

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2 Term Male Infant with Persistent Apneic Episodes

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AUTHOR DISCLOSURE Ms Kudalmana and Dr Ji have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male neonate is born at an estimated 41 3/7 weeks' gestation via vacuum-assisted vaginal delivery to a 27-year-old gravida 4, para 1 Hispanic woman. She had pregnancy-induced hypertension with her previous pregnancy. Significant family history includes a maternal uncle with seizures due to traumatic brain injury and maternal grandmother with seizures from brain tumor. Labor and delivery complications include nonreassuring fetal status with decelerations and meconium-stained amniotic fluid. The neonate's birthweight is 3,671 g and Apgar scores are 6 and 8 at 1 and 5 minutes, respectively. The neonate is "stunned" on presentation, with a weak cry, shallow breathing, and hypotonic appearance. He requires stimulation with continuous positive airway pressure support at delivery and admission to the NICU for respiratory distress.

On examination, he is sleepy but responsive. He presents with caput with normal head size, normal chest expansion symmetrically with equal breath sounds, and slight decreased tone. The remainder of the examination findings are unremarkable. Complete blood cell count and blood culture after admission show negative results after receiving 36 hours of antibiotics. The neonate continues to have multiple apneic episodes with hypoxemia, hypotonia, inconsistent weight gain, and stagnant fronto-occipital circumference. Cerebrospinal fluid shows normal cell counts, thus excluding meningitis. His initial findings on head ultrasonography and electroencephalography are normal, with no signs of seizure activity.

DISCUSSION

Diagnosis

The differential diagnosis for apnea in newborns is very broad. In term infants, apnea has several causes, including temperature instability, neurologic (birth trauma, medications, hemorrhage, seizures, central nervous system malformations), pulmonary (respiratory distress syndrome, pneumonia, pulmonary hemorrhage, anatomic malformation), cardiac (congenital heart malformation/disease, increased vagal tone), gastrointestinal (gastroesophageal reflux, abdominal distention), hematologic (anemia), infectious (sepsis, meningitis, necrotizing enterocolitis), metabolic (hypoglycemia, hypo/hypernatremia), inborn errors of metabolism, and genetic factors. (1)

Neurology recommendations for this infant included magnetic resonance imaging, which showed unremarkable results with chromosomal studies. On day 17, the neonate received formal airway evaluation due to concern for obstructive apnea, with results showing no airway malformations. On day 27 after birth, sleep study conducted due to concern for central sleep apnea demonstrated markedly severe pediatric sleep-disordered breathing with marked oxygenation instability and sleep hypoventilation. *CCHS-PHOX2B* genetic testing revealed no abnormality for congenital central hypoventilation syndrome.

Chromosome microarray revealed the diagnosis. Results showed abnormal 0.054 Mb loss of chromosome band Xq28, including part of Methyl CpG-binding protein 2 (*MECP2*) gene. This is characteristic of Rett syndrome, with the neonate considered to have *MECP2*-related neonatal encephalopathy.

On day 46, he was discharged from the hospital on nasogastric tube feeds and oxygen support.

The Condition

Rett syndrome is a progressive neurodevelopmental disorder that was believed to be exclusive to girls. In classic or typical Rett syndrome, patients have a normal neonatal period with standard developmental milestones being met between 6 and 18 months of age. (2) After this stage, patients start showing the characteristic signs and symptoms of head growth arrest, autistic features, and loss of acquired motor and language skills with stereotypic hand movements. (2)(3) Atypical Rett syndrome is differentiated as the preserved speech, early seizure, and congenital variants. (4)

MECP2 is an X-linked gene, with mutations accounting for most cases. Girls with Rett syndrome are normally heterozygous for the *MECP2* mutation with random X-chromosome inactivation, which led to the thought that this mutation was lethal in boys. (5) In boys, *MECP2* mutations are now known to produce a broad continuum of neurologic symptoms ranging from mild mental handicap to severe neonatal encephalopathy. (2)(6) Other clinical manifestations in boys include hypotonia, microcephaly, respiratory irregularities, seizures, gastrointestinal problems, and growth restriction. (7)(8)

Due to the multisystem involvement seen in Rett syndrome, there are no current targeted therapies for this disorder. Emphasis is being placed on preventive care, including nutritional management, monitoring for gastrointestinal problems, and rehabilitation therapies. Symptomatic management includes drug therapies, such as antiepileptic drugs for seizures and selective serotonin uptake inhibitors for behavioral issues. (8)

Lessons for the Clinician

- Apnea in a term infant has a wide differential diagnosis including genetic disorders.
- Clinicians should appreciate that signs and symptoms of Rett syndrome can occur on a spectrum, especially in boys.
- Medical management focuses on preventive and symptomatic care.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the significance of persistent neuromotor abnormalities in infancy (including asymmetries).

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Case 2: Term Male Infant with Persistent Apneic Episodes

Arya Kudalmana and Jianzhong Ji

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Index of Suspicion in the Nursery

3 Two-Day-Old Infant with Purulent Eye Discharge

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Beena D. Kamath-Rayne, MD, MPH,† Jennifer M. Brady, MD†

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AUTHOR DISCLOSURE Drs Zinn, Fairchild, Kamath-Rayne, and Brady have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term male infant born via spontaneous vaginal delivery has Apgar scores of 9 and 9. Two days after birth, he is noted to have copious purulent discharge with mild conjunctival edema of the left eye and mild discharge from the right eye. Erythromycin eye ointment is administered to the neonate shortly after birth per routine protocol. Maternal medical history is noncontributory, with her obstetric record showing no history of sexually transmitted infections (STIs). Warm compresses and tear duct massage are ordered based on a suspicion of nasolacrimal duct obstruction. Overnight the infant develops increased eye drainage. On physical examination, the upper eyelids appear edematous and erythematous (left greater than right) with purulent discharge bilaterally, similar to the infant in the Fig. The conjunctivae are noted to be beefy red. Eye cultures are performed and gentamicin ointment administered.

Three days after birth, in the setting of worsening bilateral edema and copious drainage, the parents are questioned in greater detail regarding their STI history. At this time, the mother discloses that 3 days before delivery she had undergone STI testing because the infant's father had been recently treated empirically for an STI. The mother is currently unaware of her test results. Further investigation reveals that the father had presented to an outside emergency department 10 days earlier for penile discharge and dysuria, and had been treated empirically with ceftriaxone and azithromycin for urethritis. The results of the father's gonorrhea and chlamydia test are negative. The mother's STI test results are found to be positive for *Neisseria gonorrhoeae*. The preliminary results of the infant's eye

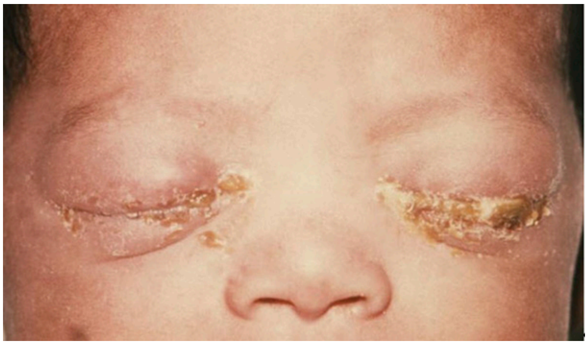

Figure. Newborn with gonococcal ophthalmia neonatorum caused by a maternally transmitted gonococcal infection. (Courtesy of Centers for Disease Control and Prevention Public Health Image Library (PHIL), identification number #3766. CDC/ J. Pledger.)

cultures reveal gram-negative diplococci. The infant is admitted to the NICU in contact isolation. A full evaluation for sepsis is initiated, including a polymerase chain reaction eye swab for chlamydia. Cefotaxime every 6 hours is started. Ophthalmology is consulted, and bacitracin ointment every 2 hours is recommended as well as balanced salt solution irrigation every 4 hours while the eye discharge is present.

DISCUSSION

Diagnosis and Hospital Course

Four days after birth, eye cultures grew *Neisseria meningitidis*. Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) test result also was positive for *N meningitidis*. Attempts at lumbar puncture were unsuccessful, while the infant's blood culture remained negative. Clinically, the infant did not demonstrate any signs of meningitis. However, due to the inability to obtain a cerebrospinal fluid specimen, infectious disease was consulted. Based on their recommendation, a 7-day course of cefotaxime treatment was started because of the inability to rule out meningitis in the setting of *N meningitidis* conjunctivitis. Staff members who came into contact with the infant were given 1 dose of ciprofloxacin prophylaxis. Several pregnant physicians who had close contact with the infant were given 1 dose of intramuscular ceftriaxone for prophylaxis. It was also recommended that the immediate family members receive prophylaxis.

The infant continued to improve and was discharged after receiving antibiotic treatment for 7 days, with recommendations for ophthalmology follow-up 1 week after discharge. After the initial treatment plans were under way, the remaining records and laboratory results of the infant's father were obtained. The father's urine culture from his previous evaluation for penile discharge was positive for *N meningitidis*.

The Condition

Neonatal conjunctivitis (NC), or ophthalmia neonatorum, is an inflammatory disease characterized by erythema, swelling, and discharge of the conjunctiva that can occur in the first 4 weeks after birth. It affects between 1.6% and 12% of all newborns. (1) NC may be a result of any of the following: bacterial infection, viral infection, or a reaction to allergens or chemicals.

Common causes of acute bacterial NC include *Chlamydia trachomatis* and *N gonorrhea* transmitted at birth. *N meningitidis* is an uncommon causative organism of acute conjunctivitis. Primary meningococcal conjunctivitis (PMC) is thought to occur because of the direct inoculation of *N meningitidis* into the conjunctival sac from an exogenous source. (2)(3)(4) PMC can precede invasive disease, serving as a mechanism for neonatal meningitis. (4)(5) Although more widespread vaccination has led to an overall decrease in invasive meningococcal disease, several studies and health clinics have reported increasing incidence of *N meningitidis* isolated from the genitourinary tract. (5)(6)(7) Due to the risks of invasive meningococcal disease, both with meningococcal and gonococcal conjunctivitis in infants, cultures should be performed of the purulent ocular discharge, blood, and cerebrospinal fluid when there is suspicion for *Neisseria* conjunctivitis. Unlike gonococcal conjunctivitis, there is no consensus on the treatment recommendations for PMC.

Previous literature shows that patients treated with topical therapy alone were 19 times more likely to develop systemic disease. (4) Therefore, systemic antibiotic therapy is necessary, and topical therapy may be used as an adjunct. Recommendations for systemic meningococcal disease are to begin empirical treatment with an extended-spectrum cephalosporin, such as cefotaxime, and switch to narrow-spectrum penicillin G once meningococcal disease is established, for a total of 5 to 7 days. (8) No consensus has been established for treatment duration.

Lessons for the Clinician

- It is important to consider *Neisseria meningitidis* when evaluating neonatal conjunctivitis, because distinguishing between *Neisseria gonorrhoeae* and *N meningitidis* has significant implications on treatment course as well as the need for prophylaxis of close contacts.
- With increased screening for sexually transmitted infections and possible increasing incidence of *N meningitidis* isolated from the genitourinary tract, there likely could be an increase in cases and/or misdiagnoses of meningococcal conjunctivitis.
- Patients with meningococcal infections should be placed in droplet isolation while instituting standard precautions until 24 hours after initiation of effective antimicrobial therapy. Chemoprophylaxis is recommended for close contacts including individuals with direct exposure to patient secretions, unprotected contact during endotracheal intubation, household contacts, or those frequently sleeping in the same dwelling as index patient.
- Chemoprophylaxis includes rifampin for 2 days for children or adults or a single dose of ciprofloxacin for adults. A single dose of azithromycin can be used with ciprofloxacin resistance. Intramuscular ceftriaxone is recommended for pregnant women.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, prevention, and pathogenesis of neonatal *Neisseria gonorrhea* infections.
- Know the clinical manifestations, diagnosis, management, and complications of neonatal *N gonorrhea* infections.
- Know the benefits and complications of eye prophylaxis (eg, obstructed nasolacrimal duct).
- Know the causes and clinical and laboratory features of acute neonatal infections of the eyes, including ophthalmia neonatorum.

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Parent Resources from the AAP at HealthyChildren.org

- Heart Disease: Reduce Your Child's Risk: https://www.healthychildren.org/English/health-issues/conditions/heart/Pages/Heart-Disease.aspx
- Screening & Treating Kids for High Blood Pressure: AAP Report Explained: https://www.healthychildren.org/English/health-issues/conditions/heart/Pages/High-Blood-Pressure-in-Children.aspx
- Detecting Urinary Tract Infections: https://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Detecting-Urinary-Tract-Infections.aspx
- Prevent Urinary Tract Infections in Children: https://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Prevent-Urinary-Tract-Infections-in-Children.aspx
- Sleep Apnea Detection: https://www.healthychildren.org/English/ages-stages/baby/sleep/Pages/Sleep-Apnea-Detection.aspx
- The Truth About Home Apnea Monitors for SIDs: https://www.healthychildren.org/English/ages-stages/baby/sleep/Pages/Home-Apnea-Monitors-for-SIDs.aspx

For a comprehensive library of AAP parent handouts, please go to the Pediatric Patient Education site at http://patiented.aap.org.

Case 3: Two-Day-Old Infant with Purulent Eye Discharge

Caitlyn K. Zinn, Ene T. Fairchild, Beena D. Kamath-Rayne and Jennifer M. Brady
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Abnormal Movements in an Infant

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Video 1. Click here to view the video.

QUESTION

Video 1

Please watch the video of a newborn. Of the following, the infant's movements are best described as (more than 1 option is possible):

A. Voluntary and normal
B. Involuntary and choreiform
C. Involuntary and tonic/clonic
D. Involuntary and athetoid
E. Involuntary and myoclonic

DISCUSSION

The infant in this video is awake and alert and exhibits the following:

- involuntary, nonrhythmic jerky movements of the shoulders and feet
- slow, irregular rhythmic movements of the fingers
- intermittent tongue thrusting
- some grimacing of the face

These movements disappeared during sleep. Also shown in the video is the infant's need for a nasal cannula and a central venous catheter. A second video (Video 2) shows the infant alternately gripping and releasing the grasp of the examiner's finger. The infant's movements shown in the videos are involuntary and choreo-athetoid.

AUTHOR DISCLOSURE Drs Chawla and Vachharajani have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. **Correct Responses:** B and D. Involuntary, choreiform, and athetoid

DISEASES WITH CHOREIFORM MOVEMENTS	ADDITIONAL FEATURES
Dyskinetic cerebral palsy, kernicterus	Athetotic movements, spasticity and dystonia (7) and chorea Hearing loss and impaired gaze (8)
Infantile bilateral striatal necrosis	Autosomal recessive Mutation of *nup62* Choreoathetosis, dystonia, spasticity Developmental regression, intellectual impairment, optic atrophy Severe bilateral striatal atrophy (9)
Infantile bronchopulmonary dysplasia (10)	Progressive occlusion of the arteries of the circle of Willis causing seizures, hemiparesis (11)
Moyamoya disease	
Lesch-Nyhan disease	Athetoid movements are often early symptoms; dystonia is also common (12)
Dopamine synthesis defects	Several types of disease Both autosomal dominant and recessive Variable age at onset and response to L-dopa treatment (13)
TSEN54-related	Autosomal recessive
Pontocerebellar	Three types (PCH2, 4, 5)
Hypoplasia (PCH)	Brainstem and cerebellar hypoplasia, microcephaly, severe cognitive impairment, seizures, poor feeding (14)
Leigh syndrome	Autosomal recessive Mutation in the E1-α polypeptide 1 of the pyruvate dehydrogenase complex 1 gene Parkinsonism, dystonia, and/or myoclonus High T2 signal in basal ganglia; elevated cerebrospinal fluid lactate/pyruvate (15)
3-Methylglutaconic aciduria type III	Autosomal recessive Mutations in the *OPA3* gene Early-onset optic atrophy and choreiform movement, later spasticity, ataxia, dementia (16)
Isolated sulfite oxidase deficiency	Autosomal recessive
	Increased urinary excretion of sulfite, thiosulfate, taurine, and sulfocysteine
	Early-onset neonatal form and late-onset form have been described
	Choreoathetosis
	Neuroimaging may show diffuse brain edema and multicystic leukoencephalopathy (17)
Nonketotic hyperglycinemia	Autosomal recessive
	Mutations in several genes in mitochondrial glycine cleavage syndrome.
	Neonatal onset
	Hypotonia, severe myoclonic epilepsy, vertical gaze palsy, profound intellectual impairment (18)
Idiopathic basal ganglia calcification–Fahr disease	Autosomal recessive
	Basal ganglia calcification, tetraplegia, severe intellectual impairment, microcephaly (19)
Alternating hemiplegia of childhood	Onset before age 18 mo
	Mutations de novo in *ATP1A* gene
Drug-induced chorea	Episodes of hemiplegia, dystonia, or chorea affecting either side and disappearing with sleep (20)
	Benzodiazepines (diazepam), antihistamine (cyproheptadine), hormones (levothyroxine, estrogen), central nervous system stimulants (amphetamine, cocaine, methylphenidate) (21)

Video 2. Click here to view the video.

During an examination of a neonate with abnormal movements, it is helpful to characterize the movements by the following:

- Voluntary versus involuntary
- Rhythmic/regular versus nonrhythmic/irregular
- Purposeful versus nonpurposeful
- Slow versus rapid
- Part of the body involved

The abnormal movement chorea (from the Greek word "choros" and from the Latin word "choreus," both meaning dance) is a type of involuntary movement collectively referred to as a movement disorder. It typically involves the hands, feet, and face. In 1686, Thomas Sydenham, an English physician, was the first clinician to provide the most thorough description of chorea in children, and, thus, the condition is often referred to as Sydenham chorea. (1) The abnormal movements of chorea are involuntary, irregular, nonrhythmic, nonpurposeful, abrupt, rapid, and unsustained; the movements appear to flow from one body part to another, also known as dancelike movements. (2) Typically, the movements often appear jerky and involve the distal muscle group.

The term *athetosis* is derived from the Greek meaning "without position or place," describing the patient's inability to maintain a stable posture. Athetosis involves repeated movements of the same regions of the body. (3) The abnormal movements of athetosis are involuntary, nonrhythmic, nonpurposeful, and slow. In contrast to chorea, the movements of athetosis are not discrete and appear to flow continuously. (4) Athetosis typically involves the upper limbs. In the videos, the jerky movements of the infant's shoulders and feet are consistent with chorea, and the infant's slow rhythmic movements of the fingers are consistent with athetosis.

Although the exact anatomical location responsible for choreiform movements is inadequately understood, the most robust connection between anatomy and clinical presentation is found at the subthalamic nucleus in the basal ganglia of the brain, where hemiballism and hemichorea can originate from acute causes (eg, infarcts) or from more gradual lesions (such as an arteriovenous malformation or a tumor). Injury to other basal ganglia structures is less likely to lead to chorea. Damage to the putamen and globus pallidus externa have also been associated with choreiform movements. (5) Dopaminergic neurotransmission is believed to play an important role in chorea because the most effective pharmacologic control is achieved by medications that deplete or block these pathways (6)

There are various etiologies of chorea in infancy, which are summarized in the Table. The management of infants with chorea is based on etiology. In cases of drug-induced chorea, discontinuing the offending agent can stop the movements. For persistent chorea, management with agents that decrease the dopaminergic activity (ie, dopamine receptor-blocking agents), such as phenothiazines (chlorpromazine), butyrophenones (haloperidol), pimozide, (22) or tetrabenazine, (23)(24) can suppress the movements.

The jerkiness of the infant's activity makes voluntary movements unlikely. This infant is unlikely to have tonic/clonic seizures because they would occur with regular frequency and typically do not involve the fingers. Myoclonus is an involuntary movement caused by contraction of a group of muscles. Infantile myoclonic movements can be jerky but are typically not sustained. Infants with sleep myoclonus are usually asleep. Infants with West syndrome (ie, infantile spasms) have clustered spasms during infancy with extension or flexion of the neck, arms, and legs; patients with tuberous sclerosis are at increased risk for infantile spasms.

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ANSWER KEY FOR JUNE 2018 NEOREVIEWS

Neonatal Acute Kidney Injury: 1. B; 2. E; 3. C; 4. A; 5. D.

Diagnosis and Management of Urinary Tract Infections in Premature and Term Infants: 1. A; 2. C; 3. A; 4. D; 5. C.

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Attempt at Trial of Labor After Cesarean Delivery in Late-Term Gestation with Oligohydramnios

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal values for arterial umbilical cord gas values and indications of acidosis are defined in the Table.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

AUTHOR DISCLOSURE Drs Aluko and Spiel have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. **Arterial Umbilical Cord Gas Values**

	pH	Pco$_2$ (mm Hg)	Po$_2$ (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤−10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤−10
Metabolic acidosis	<7.20	<60	Variable	≥−10
Mixed acidosis	<7.20	>60	Variable	≥−10

**Normal ranges from* Obstet Gynecol Clin North Am. *1999;26:695.*

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

  Absent: Amplitude range is undetectable
  Minimal: Amplitude range is greater than undetectable to 5 beats/min
  Moderate: Amplitude range is 6–25 beats/min
  Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation.

Examples of these tracings include any of the following:

  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:

  - Absent variability with any of the following:
    - ■ Recurrent late decelerations
    - ■ Recurrent variable decelerations
    - ■ Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol*. 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

History

A 32-year-old gravida 2 para 1-0-0-1 woman presented to the maternal fetal medicine unit at gestational age 41 weeks and 2 days for late-term testing. She underwent ultrasonography, which confirmed a cephalic fetus estimated to weigh 3,918 g (79%). The amniotic fluid index was 2.9 cm, with a maximum vertical pocket of only 1.5 cm, consistent with oligohydramnios. Results of her antenatal testing were otherwise reassuring, with appropriate fetal movements, normal fetal tone, and regular fetal breathing by ultrasonography, resulting in 6/8 biophysical testing (minus 2 points for oligohydramnios). Because the patient was at late-term gestation with a new diagnosis of oligohydramnios, delivery was recommended. Her obstetric history was notable for a previous low transverse cesarean delivery in the setting of FHR tracing abnormalities during the second stage of labor. Otherwise, she had a benign medical history and a negative screen for group B *Streptococcus* colonization. She was counseled on her options for delivery: a repeated cesarean delivery or induction of labor. She was motivated to attempt a vaginal delivery.

Case Progression

On arrival at the labor and delivery unit, her cervical examination showed 2-cm dilation, 60% effacement, −2 station, soft consistency, and mid-positioning. Although her cervix was dilated, the patient was comfortable and not in labor. Given her previous hysterotomy, use of misoprostol for induction of labor was contraindicated because of the increased risk of uterine rupture. Therefore, her induction was initiated with an intracervical Foley balloon, which was inflated with saline. Risks and benefits of these induction agents were reviewed with the patient before use. Figure 1 exemplifies the FHR tracing on admission. This tracing represents a reactive tracing, which completes the fetal testing of 8/10, when combined with the biophysical profile, thus overall reassuring.

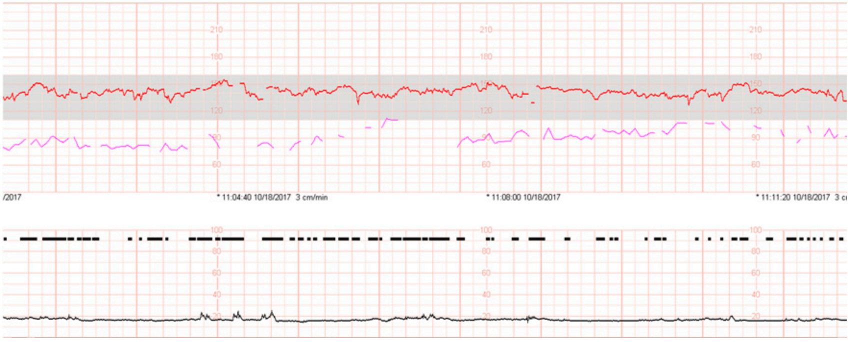


Figure 1. Electronic fetal monitoring strip 1.

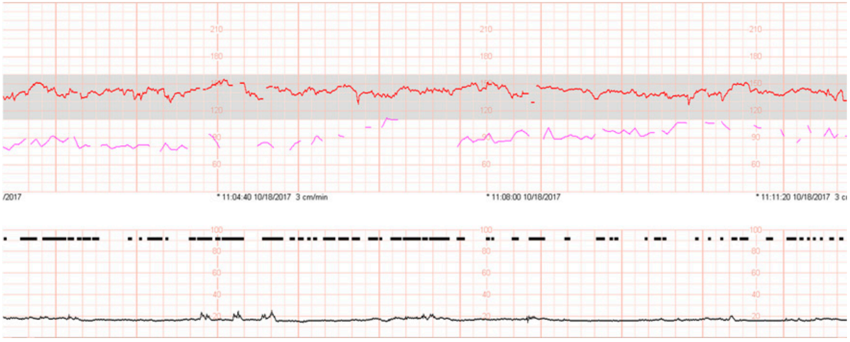
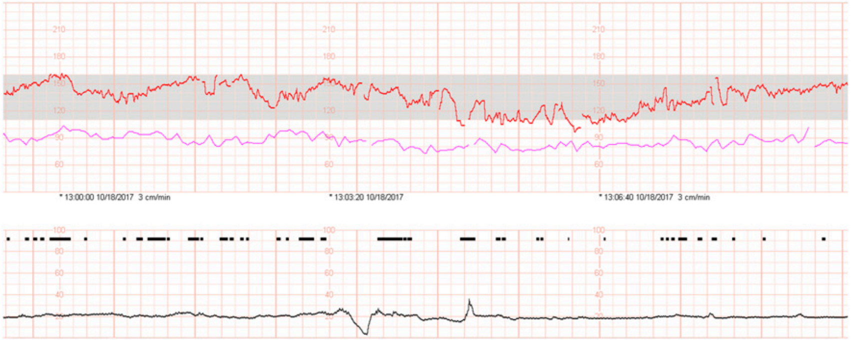


Figure 1. Electronic fetal monitoring strip 1.

Findings from EFM strip 1 are as follows:

- Variability: Moderate
- Baseline rate: 130 beats/min
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category I
- Differential diagnosis: Reactive and reassuring FHR tracing
- Action: Induction of labor was initiated

Risks and benefits were reviewed with the patient, and an intravenous oxytocin infusion was added to induce labor. Almost immediately after this induction agent was started, the patient began to have mild, irregular contractions that were not all traced on tocometry. Figure 2 represents the FHR tracing after oxytocin initiation.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* 13:06:40 10/18/2017 3 cm/min
100
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Figure 2. Electronic fetal monitoring strip 2.

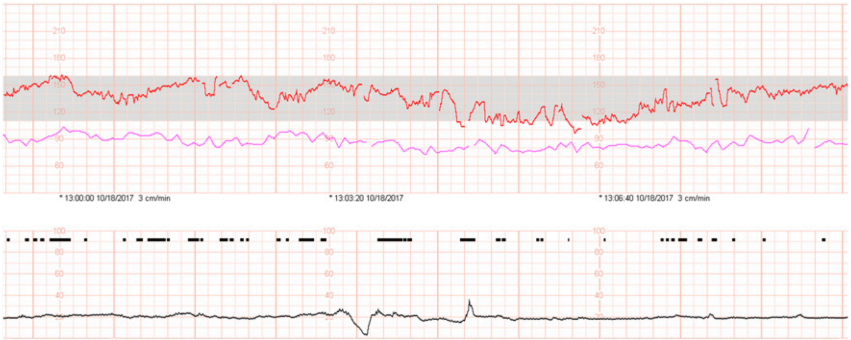

Figure 2. Electronic fetal monitoring strip 2.

Findings from EFM strip 2 are as follows:

- Variability: Moderate
- Baseline rate: 140 beats/min
- Episodic patterns: Prolonged deceleration
- Periodic patterns: None
- Uterine contractions: Rare
- Interpretation: Category II
- Differential diagnosis: A prolonged deceleration signifies a disruption in fetal oxygenation for longer than 2 minutes; this can be due to placental abruption, umbilical cord compression, tachysystole, tetanic uterine contractions, uterine rupture, or rapid change in fetal station.
- Action: Oxytocin was continued; the physician was notified; no additional interventions were necessary because the FHR spontaneously returned to baseline

The goal of obstetrical management in a category II FHR tracing is to optimize blood flow to the uterus to improve oxygenation to the fetus. Ongoing fetal evaluation by external continuous monitoring is recommended. Prolonged decelerations should prompt urgent assessment because the cause of fetal hypoxia needs to be corrected as soon as possible. Maternal hypotension, vaginal bleeding, or worsening abdominal pain may raise suspicion for placental abruption or uterine rupture, especially in the setting of a previous hysterotomy. Intravenous fluids or vasopressors can be used to treat maternal hypotension, if present. A cervical examination should be performed to ensure that there is no loss of fetal station (a sign of uterine rupture), to evaluate for rapid labor progression, and to exclude umbilical cord prolapse. Maternal repositioning to either the lateral recumbent or hands-and-knees position can be attempted to increase placental perfusion and relieve potential umbilical cord compression if the FHR deceleration does not resolve. Maternal oxygen administration may be used as well. If tachysystole or a tetanic contraction is suspected, discontinuation of intravenous oxytocin may be necessary. Alternatively, administration of a tocolytic agent such as terbutaline facilitates rapid cessation of contractions and allows for FHR recovery. Immediate cesarean delivery is indicated if the FHR deceleration persists despite these maneuvers and labor has not progressed sufficiently.

After this event, the patient continued to have intense and frequent contractions. The Foley balloon spontaneously expelled. The woman then underwent artificial rupture of membranes, and repeated cervical examination demonstrated 5-cm dilation, 80% effacement, and −1 station. She requested epidural placement. The FHR tracing at this time is represented in Fig 3.

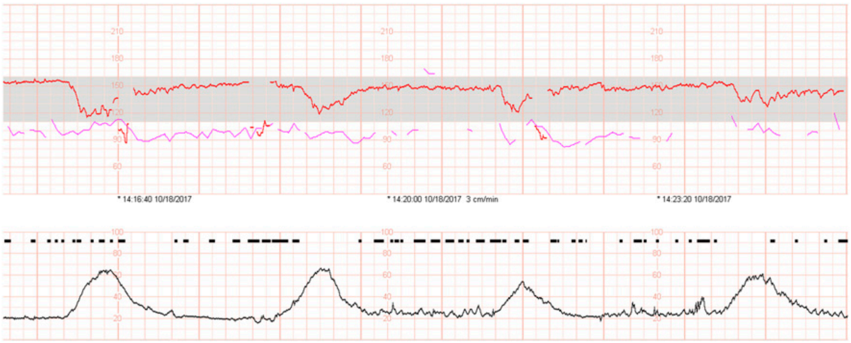

Figure 3. Electronic fetal monitoring strip 3.

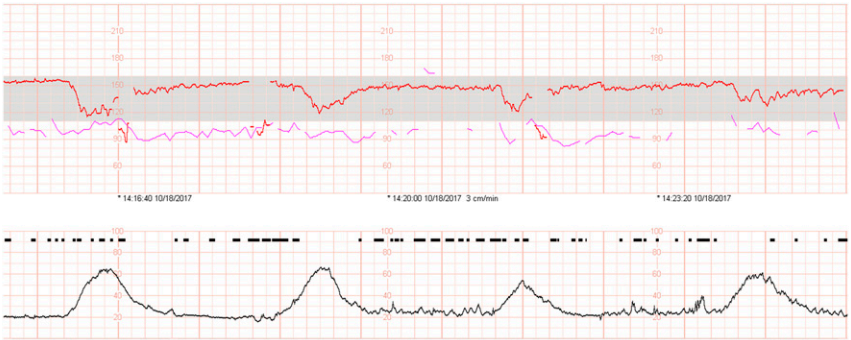

Figure 3. Electronic fetal monitoring strip 3.

Findings from EFM strip 3 are as follows:

- Variability: Moderate
- Baseline rate: 150 beats/min
- Episodic patterns: None
- Periodic patterns: Recurrent variable decelerations
- Uterine contractions: Every 2 to 3 minutes
- Interpretation: Category II
- Differential diagnosis: Our patient's variable decelerations are likely due to low amniotic fluid volume given her diagnosis of oligohydramnios, compounded by her recent artificial rupture of membranes; a nuchal cord, umbilical knot, and umbilical cord prolapse can also result in variable decelerations
- Action: The patient's cervix was examined and she was repositioned

Variable decelerations result from transient umbilical cord compression and can be either intermittent (associated with <50% of contractions) or recurrent (associated with >50% of contractions). Whereas intermittent variable decelerations are benign and can be expectantly managed, recurrent variable decelerations require intervention. A cervical examination should be performed to rule out an umbilical cord prolapse, followed by maternal repositioning in an attempt to alleviate cord compression. If the patient continues to have recurrent variable decelerations, an amnioinfusion can be considered. In this specific scenario, uterine rupture should also be considered, and a cervical examination would be helpful to determine whether there is a loss in fetal station. The patient's cervical examination demonstrated 6-cm dilation, 90% effacement, and −1 station. The variable decelerations resolved with repositioning, and the induction was continued with intravenous oxytocin. Her cervix made further changes to 9-cm dilation, 90% effacement, and −1 station.

Over the next 4 hours, our patient's cervical examination findings remained unchanged, and there was increasing concern for arrest of dilation. In addition, the patient developed a fever. An intrauterine pressure catheter was placed to assess the adequacy of her uterine contractions (Fig 4).

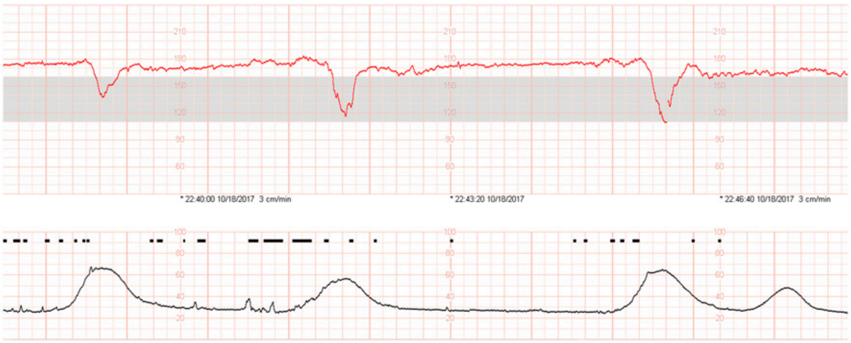
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Figure 4. Electronic fetal monitoring strip 4.

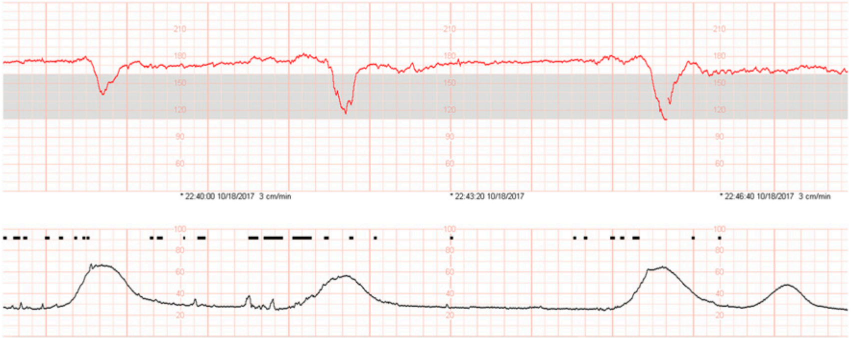


Figure 4. Electronic fetal monitoring strip 4.

Findings from EFM strip 4 are as follows:

- Variability: Moderate
- Baseline rate: 170 beats/min
- Episodic patterns: None
- Periodic patterns: Recurrent variable decelerations
- Uterine contractions: Contractions every 3 to 4 minutes; 120 Montevideo units (MVU)
- Interpretation: Category II
- Differential diagnosis: In the setting of a maternal fever, fetal tachycardia is most likely due to chorioamnionitis; less likely, but also possible, are medication adverse effects, fetal hypoxia, fetal anemia, and fetal arrhythmia
- Action: The patient was treated for chorioamnionitis with antibiotics and antipyretics.

Chorioamnionitis, or intra-amniotic infection, affects 1% to 4% of pregnancies (1) and can present with fever, maternal tachycardia, fetal tachycardia, foul-smelling amniotic fluid, and uterine fundal tenderness. It results from a polymicrobial infection caused by ascending vaginal and enteric flora, and it is typically treated with intravenous ampicillin and gentamicin, as was the case in this patient.

A new diagnosis of chorioamnionitis should prompt evaluation of the patient's labor curve to ensure that progress is being made toward delivery. Diagnosis of arrest of dilation requires the patient to have greater than or equal to 6-cm dilation with membrane rupture and 1 of the following: 1) greater than or equal to 4 hours of adequate contractions without cervical change or 2) greater than or equal to 6 hours of inadequate contractions without cervical change. (2) Contractions are adequate if greater than 200 MVU. Although our patient had inadequate contractions (120 MVU), her cervix had not changed in 4 hours and, therefore, had not yet met the criteria for arrest of dilation. The patient was motivated for a vaginal delivery, and given her overall reassuring status, labor was allowed to continue. The recurrent variable decelerations resolved with repositioning, and the decision was made to continue her induction with up-titration of intravenous oxytocin. Figure 5 shows the FHR tracing pattern that ensued.

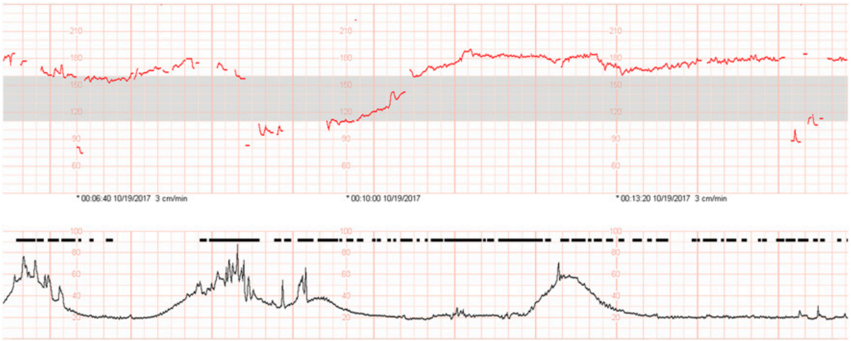
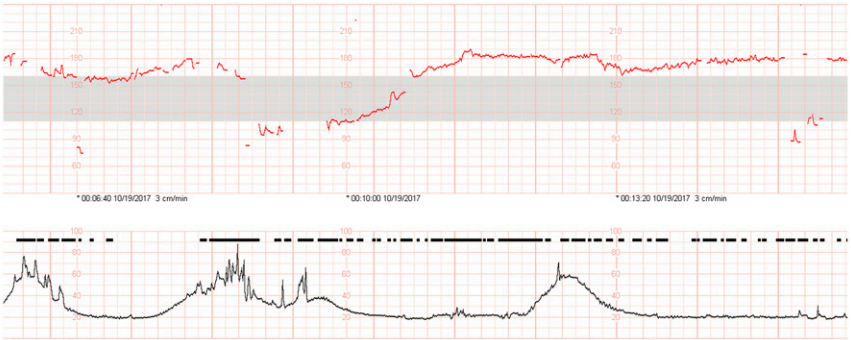


Figure 5. Electronic fetal monitoring strip 5.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* 00:10:00 10/19/2017
* 00:13:20 10/19/2017 3 cm/min
100
80
60
40
20

Figure 5. Electronic fetal monitoring strip 5.

Findings from EFM strip 5 are as follows:

- Variability: Moderate
- Baseline rate: 170 beats per min
- Episodic patterns: None
- Periodic patterns: Late decelerations
- Uterine contractions: Contractions every 1 to 4 minutes; 100 MVU
- Interpretation: Category II
- Differential diagnosis: Includes maternal hypotension or hypoxia and uteroplacental insufficiency
- Action: Isolated late decelerations that spontaneously return to baseline, as was the case here, may not require any additional interventions; if late decelerations become recurrent, maneuvers to reduce fetal hypoxia by improving uteroplacental perfusion should be considered; as described previously herein, this can be achieved by maternal repositioning, administration of supplemental oxygen or intravenous fluid bolus, and temporarily discontinuing intravenous oxytocin.

An additional 2 hours passed without any cervical change, and the patient failed to reach 10 cm of cervical dilation. She was diagnosed as having an arrest of the first stage of labor. Additional diagnosis included chorioamnionitis with fetal tachycardia. Due to the arrest disorder and the return of the recurrent variable decelerations with intermittent late decelerations, a cesarean delivery was advised, and the patient agreed.

Outcome

The patient underwent an uncomplicated repeated low transverse cesarean delivery of a liveborn male infant from the occiput posterior position. The infant weighed 3,800 g and had Apgar scores of 8 and 9 at 5 and 10 minutes, respectively. Intraoperative findings were notable for an anterior placenta as well as a 3- to 4-cm uterine window in the lower uterine segment. Placental pathology confirmed the diagnosis of acute chorioamnionitis.

DISCUSSION

In recent years, attention has focused on reducing the cesarean delivery rate in the United States as a public health measure. As a result, women are increasingly electing for trial of labor after cesarean delivery (TOLAC). Much of the benefit of a vaginal birth after cesarean delivery (VBAC) is related to avoidance of major intra-abdominal surgery, which carries the risks of hemorrhage, blood transfusion, infection, and venous thrombosis, among others. In addition, a successful VBAC has implications for future pregnancies because it reduces maternal morbidity associated with multiple cesarean sections, including abnormal placentation, bowel injury, cystotomy, and hysterectomy.

Counseling regarding mode of delivery for a patient with a previous cesarean delivery involves discussion surrounding previous indication for surgery, specifically whether recurrent need for cesarean delivery is likely. Providers should also take into consideration the type of hysterotomy performed, as well as the likelihood of success based on maternal characteristics, including previous vaginal birth, age, body mass index, race and ethnicity, and short-interval delivery. Predicting the likelihood of successful vaginal delivery can be estimated with the Maternal-Fetal Medicine Units online calculator, which is based on a nomogram and takes into account all the aforementioned factors. (3) In addition, the risk of uterine rupture in labor must be discussed. All patients undergoing a TOLAC should be counseled on the risk of uterine rupture and uterine dehiscence; these complications account for most neonatal and maternal morbidity due to TOLAC. Our patient had a previous low transverse cesarean delivery, which portends a 0.5% to 0.9% risk of uterine rupture. (4) It must also be reviewed with the patient that a failed TOLAC is associated with more complications than an elective repeated cesarean delivery. Not all women are ideal candidates for TOLAC, and all patients should undergo assessment for the likelihood of VBAC. Our patient had a predicted success rate for VBAC of 60% to 70% using this calculator.

As described previously herein, in the setting of nonearly decelerations in patients undergoing TOLAC, there should always be high suspicion for uterine rupture. Intraoperatively, our patient was found to have a uterine window (uterine dehiscence), which could have contributed to the FHR abnormalities discussed herein. Uterine scar dehiscence can ultimately progress to uterine rupture, but it is difficult to predict before delivery due to imaging limitations. In women undergoing TOLAC, nonreassuring fetal heart status may prompt a repeated cesarean delivery, as it is a predictor of uterine rupture or dehiscence. (5)(6) Although FHR patterns associated with uterine rupture have been characterized, there is limited information on how uterine dehiscence affects the FHR during labor. Some studies indicate that in the time preceding uterine rupture it is more common to note recurrent late decelerations and terminal bradycardia. (7)(8) Other studies have cited variable decelerations, uterine tachysystole, and reduced baseline variability as potential warning signs of uterine rupture. (8)(9)(10)(11)

Although the maternal and neonatal consequences of uterine rupture have been described in the literature, the implications of uterine dehiscence remain unclear. In 1 retrospective study, women with a history of pregnancy complicated by uterine scar dehiscence were at increased risk for iatrogenic preterm delivery, low birthweight, and peripartum hysterectomy. Interestingly, in this particular study the rates of uterine rupture were similar in women with and without a history of uterine dehiscence. (12) All of the above was taken into account when counseling our patient on her future pregnancies.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the complications and effects of chorioamnionitis in the mother and the fetus.
- Know the indications for and perinatal complications of operative vaginal delivery (forceps, vacuum extraction, etc) and of vaginal delivery after cesarean delivery.

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Attempt at Trial of Labor After Cesarean Delivery in Late-Term Gestation with Oligohydramnios

Ashley Aluko and Melissa Spiel

NeoReviews 2018;19;e361
DOI: 10.1542/neo.19-6-e361

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A Term Neonate with a Malpositioned Umbilical Artery Catheter Tip

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**Department of Pediatrics, Division of Neonatology, Cohen Children's Medical Center, New Hyde Park, NY*

THE CASE

A term neonate with respiratory distress receiving endotracheal mechanical ventilation undergoes placement of umbilical venous and arterial catheters.

Prenatal and Birth Histories

- Full-term female neonate
- Born to a 27-year-old gravida 6, para 5, white woman
- Prenatal maternal laboratory screening unremarkable
- Emergent cesarean delivery for fetal tachycardia with recurrent late decelerations at the local community hospital
- Meconium-stained amniotic fluid noted at delivery
- Infant had poor tone and no spontaneous respiratory effort at delivery
- Infant was dried, positioned, and suctioned
- Positive pressure ventilation was administered in the delivery room followed by continuous positive airway pressure due to respiratory distress
- Apgar scores: 4 and 8 at 1 and 5 minutes, respectively

Presentation

The infant was admitted to the community hospital NICU. Endotracheal intubation was performed at 2 hours of age for increasing oxygen requirements and respiratory failure. Conventional mechanical ventilation was initiated with a fraction of inspired oxygen of 1.0. Chest radiography suggested meconium aspiration syndrome. Exogenous surfactant was administered and umbilical vein catheter (UVC) was placed. On radiography, the UVC tip was visualized in the liver and the catheter readjusted to a low-lying position and secured at 5 cm. The umbilical artery catheter (UAC) placement was unsuccessful. Blood culture specimen was obtained and treatment with ampicillin and gentamicin initiated. Persistent pulmonary hypertension of the newborn was suspected based on a 10% difference in pre- and postductal oxygen saturation; at 3 hours of age, inhaled nitric oxide (iNO) of 20 parts per million (ppm) was initiated for an oxygen index of 18 determined on a radial arterial blood gas.

The infant was transferred to a level IV NICU for further evaluation and consideration of extracorporeal membrane oxygenation. Upon arrival at the level IV NICU, the neonate was placed on high-frequency oscillatory ventilation and iNO was continued at 20 ppm. Echocardiography showed pulmonary hypertension based on right ventricular systolic pressures estimated at near-systemic level. The low-lying UVC was replaced with a new UVC. At the same time, a UAC was placed. Both catheters passed easily on first attempt with good blood return.

AUTHOR DISCLOSURE Drs Haggerty and Kurepa have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

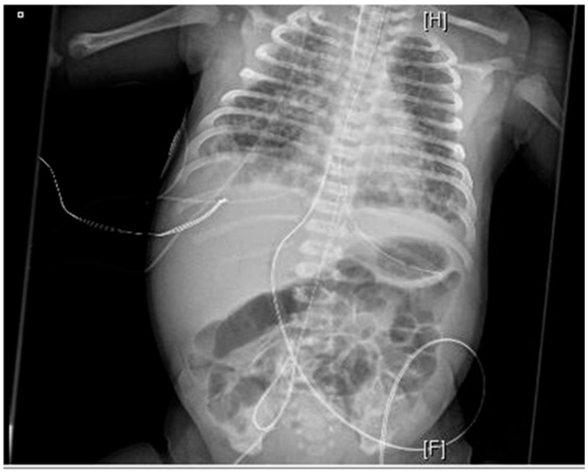

Figure 1. Radiography of the chest and abdomen.

Radiography of the chest and abdomen showed UVC tip in the right atrium and malpositioned UAC tip (Fig 1).

Physical Examination

- Normal status for gestational age

DIFFERENTIAL DIAGNOSIS OF MALPOSITIONED UMBILICAL ARTERY CATHETHER

- Placement in (1):
  - Femoral artery
  - Gluteal artery
  - Renal artery
  - Celiac plexus
- Perforation through umbilical artery (2)
- Catheter folding or coiling

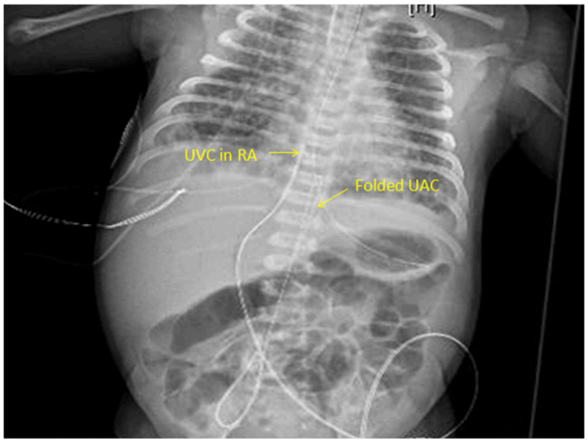

Figure 2. Radiography of the chest and abdomen showing UVC tip in the right atrium and distal UAC coiled in aorta.

ACTUAL DIAGNOSIS

Thoracoabdominal radiography showed that the UVC tip was located in the right atrium and that the distal UAC was coiled in the aorta (Fig 2). Point-of-care ultrasonography (POC-US) of the heart and abdomen confirmed that the UVC tip was in the right atrium and UAC was folded in the descending aorta (Fig 3).

CASE PROGRESSION

Under sterile conditions and real-time ultrasound guidance, the UAC was carefully retracted until it uncoiled, then advanced to above the celiac artery. The UVC tip was retracted to the cavoatrial junction also by using POC-US. Initial placement of UAC and UVC and postprocedure radiography took 40 minutes. Correction with POC-US took less than 10 minutes.

The infant tolerated weaning of respiratory support and underwent extubation at 6 days of age and weaned to room air at 10 days. The infant was discharged from the hospital at 23 days of age in room air and full oral feedings. Echocardiography before discharge showed resolution of the pulmonary hypertension.

WHAT THE EXPERTS SAY

Umbilical catheterization is an integral part of the care of sick newborns in the first week after birth.

Umbilical venous catheters are indicated mainly for the administration of fluids, parenteral nutrition, and medications. They are also used for exchange transfusions, central venous pressure monitoring, and diagnosis of total anomalous pulmonary venous return below the diaphragm. (3) Complications of malpositioned UVCs include infection,

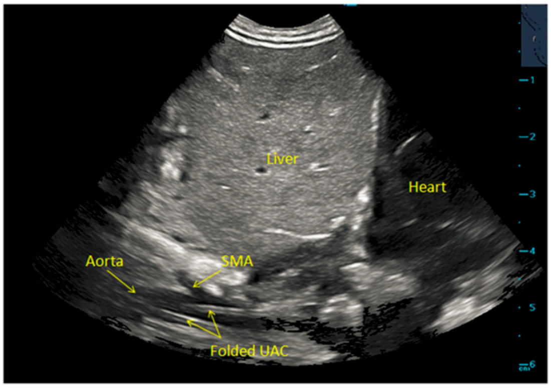

Figure 3. Ultrasound with sagittal view of the aorta showing folded distal tip of the UAC.

abscess, hepatic necrosis, laceration, cysts, colonic perforation, ascites, pleural effusion, hydrothorax, arrhythmias, myocardial perforation, pericardial effusion and tamponade, pneumopericardium, thrombosis, or embolization. (3)(4)(5)

Umbilical arterial catheters are used for arterial blood pressure monitoring, frequent or continuous measurement of arterial blood oxygen tension, frequent blood sampling, exchange transfusion, and angiography. (6) They can also be used for emergency administration of fluids and medications in situations in which venous access is unavailable. Complications of umbilical arterial catheterization are rare but potentially serious, and include infection, hemorrhage, hypoglycemia, bladder rupture, bowel perforation, necrotizing enterocolitis, paraplegia, loss of limb, hypertension, umbilical artery rupture, aortic dissection, aneurysm and/or rupture, thrombosis, and embolization. (6)(7) As expected, the risk of central line complications is increased with malpositioned catheters.

For UAC placement, the high position is recommended. This high distal tip position is in the descending aorta above the diaphragm. (6)(8) A meta-analysis by Barrington found that high positioning leads to fewer ischemic complications compared with low positioning. (8) Low positioning at the level of lumbar vertebrae L3 to L4 should be used only in rare cases when there is a critical need for arterial access and high positioning is unsuccessful. (6)

At the authors' institution, the neonatal fellows and neonatal nurse practitioners perform umbilical catheterization. When the catheter is inserted, it is blindly advanced to a predetermined length calculated by the weight-based regression equation described by Shukla and Ferrara. (9) Catheter position is then confirmed with postprocedure radiography. For UAC placement, optimal placement is in the high position, corresponding to thoracic vertebral levels T6 to T9, and for UVC placement, it is at the level of the inferior vena cava–right atrial junction. If adjustments are necessary, catheter position is confirmed again on radiography. Recently, our institution has begun to perform adjunct real-time POC-US–guided central catheter placement for specific cases. At present, the authors' use of POC-US is reserved for more challenging cases in which catheter position on radiography may be ambiguous, for very unstable patients with time constraints, or for patients who may be adversely affected by repeated manipulation.

The use of ultrasonography to determine umbilical catheter position was reported as early as 1983 by Garg et al, but it is still not the standard of care. (10) As availability of POC-US has increased, several recent studies have examined its accuracy and timeliness. In 2011, a randomized controlled trial by Fleming and Kim compared the use of ultrasound-guided UVC placement versus the standard procedure of advancement to a precalculated distance followed by postprocedure radiography. Ultrasound guidance reduced procedure time by an average of 64 minutes, as well as decreased the number of catheter manipulations. In addition, ultrasound guidance can identify incorrectly positioned catheters in real-time so that they can be immediately removed or adjusted, thus potentially reducing severe complications. (11) Simanovsky et al prospectively compared UVC catheter tip placement using both ultrasonography and radiography in 75 neonates, and concluded that ultrasonography is reliable for detecting catheter malposition. (12) In 2012, Michel et al compared ultrasonography to radiography for the detection of UVC tip position and found that it was more sensitive and specific (93.3% and 95.6% vs 66.7% and 63.0%, respectively). (13)

In 2016, Nguyen performed a literature review of 12 studies describing ultrasound-guided central venous catheter insertion as well as postinsertion ultrasonographic confirmation of the catheter tip position. He concluded that ultrasonography can be a complementary technique for central venous catheter placement but the evidence is inadequate for ultrasonography to replace radiography for catheter tip position confirmation. (14) Nevertheless, in 2017 a prospective observational study performed on 65 very-low-birthweight infants suggested, yet again, that radiography may be imprecise in determining umbilical venous catheter position. Only 44% of UVCs that were in the appropriate position on radiography were found to be in optimal position using ultrasonography. This study also examined rates of UVC migration during the first week of age. They found that 50% of infants experienced UVC migration. This was attributed to drying of the Wharton jelly and shrinking of the umbilical cord and/or changes in abdominal girth. Using POC-US for serial assessments of catheter tip position can obviate the need for repeated radiography. (15)

This case supports the use of real-time POC-US as a valuable adjunct technique for both UAC and UVC placement.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the causes and clinical manifestations of catheter complications of parenteral nutrition.
- Know the pathogenesis and complications of umbilical arterial catheter–related thrombi.

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A Term Neonate with a Malpositioned Umbilical Artery Catheter Tip

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Answer Key appears on page e421.

Acyanotic Congenital Heart Disease: Left-to-Right Shunt Lesions

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Education Gap

An understanding of the pathophysiology, diagnosis, and appropriate initial management of acyanotic congenital heart disease is needed to appropriately care for infants in the NICU.

Abstract

Acyanotic congenital heart diseases or left-to-right shunting lesions are the most common form of congenital heart disease. Although most resolve spontaneously, many will remain hemodynamically significant, particularly in the premature infant. Understanding the difference in pathophysiology, diagnosis, and management between the term and preterm infant is imperative to minimize the risk of secondary organ dysfunction and ensure proper growth and development.

Objectives

After completing this article, readers should be able to:

1. Explain the pathophysiology, initial presentation, and management of left-to-right pre-tricuspid shunt lesions.
2. Explain the pathophysiology, initial presentation, and management of left-to-right post-tricuspid shunt lesions.
3. List the genetic mutations associated with the different left-to-right shunt lesions.
4. Differentiate the effects of these lesions on term and preterm infants.

AUTHOR DISCLOSURE Drs Colombo and McCulloch have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ASD	atrial septal defect
AVSD	atrioventricular septal defect
CHD	congenital heart disease
ECG	electrocardiography
PDA	patent ductus arteriosus
PVR	pulmonary vascular resistance
Qp	pulmonary blood flow
Qs	systemic blood flow
SVR	systemic vascular resistance
VSD	ventricular septal defect

INTRODUCTION

Congenital heart disease (CHD) is the most common genetic abnormality, with an incidence that increases from approximately 8 per 1,000 term births to 12.5 per 1,000 premature births. (1)(2) More important, however, are the significantly increased hemodynamic consequences of CHD in preterm infants compared with their term peers. This review will focus on acyanotic CHD defined as an anatomic connection between the pulmonary and systemic circulations in which oxygenated systemic blood flow on the left side of the heart shunts to the partially deoxygenated pulmonary blood flow on the right side of the heart. The vast array of acyanotic heart lesions will be grouped into 2 physiologic subtypes of pre-tricuspid valve and post-tricuspid valve shunting. Further consideration will be given to gestational age when appropriate.

PRE-TRICUSPID VALVE SHUNTS

The physiologic distinction of pre-tricuspid valve shunts describes shunting across an atrial septal defect (ASD) during ventricular diastole and atrial systole. The *direction* of flow across an atrial communication is dictated by differences in ventricular compliance. Ventricular compliance can change when chronic atrial contraction occurs into a ventricle that has become stiff and noncompliant either from myopathic changes (ie, hypertrophic cardiomyopathy) or from chronically elevated afterload (ie, pulmonary/aortic valve stenosis or elevated pulmonary or systemic vascular resistance).

Shortly after birth, ASD shunt magnitude is low because neonatal right ventricular stiffness and compliance are very similar to those in the left ventricle. With physiologic declines in pulmonary vascular resistance, compensatory in utero right ventricular hypertrophy regresses, resulting in a more compliant right ventricle and atrium. This allows a progressive left-to-right increase in ASD shunt volume that is further pronounced with larger defect size. (3) ASDs are considered volume-loading defects to the right heart (as opposed to pressure-loading defects; see Post-Tricuspid Valve Shunts section), with larger defects producing right atrial and ventricular dilation.

Incidence

Excluding patent foramen ovale, which persists in up to 35% of adults, ASDs exist in approximately 1 in 1,500 children, comprise 6% to 10% of all cardiac anomalies, (4) and are the most commonly recognized mutation in nonsyndromic CHD. (5) Although ASDs frequently occur with other congenital heart lesions, isolated ASDs have been associated with *NKX2.5*, *GATA4*, *GATA6*, and *TBX20* mutations. Mutations in the *TXB5* gene are associated with Holt-Oram syndrome.

Several anatomic classifications of atrial defects can occur in utero when the septum primum and septum secundum do not appropriately fuse with each other, the endocardial cushions, and posterior aspect of the atria. Ostium secundum type defects compose 75% of all ASDs and are essentially identical to a patent foramen ovale with the major distinction being size. (4) The foramen ovale is a critical connection maintained throughout fetal life, directing oxygenated ductus venosus blood across its opening to the left atrium, left ventricle, preductal aortic vessels, and the developing brain. Primum ASDs exist in the setting of atrioventricular septal defects (AVSDs) but their physiologic presentation is typically determined more by the associated lesions. Sinus venosus type ASDs comprise 4% to 11% of all ASD types and are commonly associated with anomalous return of at least 1 pulmonary vein, resulting in a significantly larger left-to-right shunt. (6) Coronary sinus ASDs not only produce ASD physiology but are commonly associated with systemic desaturation as they functionally "unroof" the coronary sinus, adding markedly desaturated blood into the left atrium.

Diagnosis

ASDs are rarely associated with clinical findings in the term neonate. At 2 to 3 years of age, classic findings include a widely split S2 and a systolic ejection murmur along the left sternal border because of increased flow across the pulmonary valve. Echocardiography is the diagnostic tool of choice (Fig 1). Chest radiography may show an enlarged cardiac silhouette and increased pulmonary vascular markings, but this can be difficult to appreciate in an infant with lung disease. Electrocardiography (ECG) will show right ventricular hypertrophy and right axis deviation, but this is true in all newborns and is usually not helpful.

Management

Term neonates with isolated ASDs are typically asymptomatic and rarely require intervention. Should the patient develop significant signs of congestion with increased work of breathing, tachypnea, hepatomegaly, and poor growth, diuretics are the first-line treatment. As such, ASD closure is not common until at least 2 years of age, with both device closure in the catheterization laboratory and surgical closure having excellent results. (7)(8)

Premature Infants

The premature infant with chronic lung disease represents a unique challenge. When subjected to chronic hyperoxia and positive pressure ventilation, the immature lung parenchyma exhibits alveolar simplification. (9) The subsequent reduced number of alveoli renders these infants particularly sensitive to any increase in pulmonary blood flow, particularly when coupled with aspiration, inflammation, or acquired pulmonary vein stenosis, all of which result in congestion from increased intra-alveolar fluid. Therefore, premature infants not following the expected perinatal course (ie, respiratory distress out of proportion to their lung disease) who have an ASD deemed amenable to device closure in the cardiac catheterization laboratory should be considered for this therapy to improve outcomes. (10)(11)

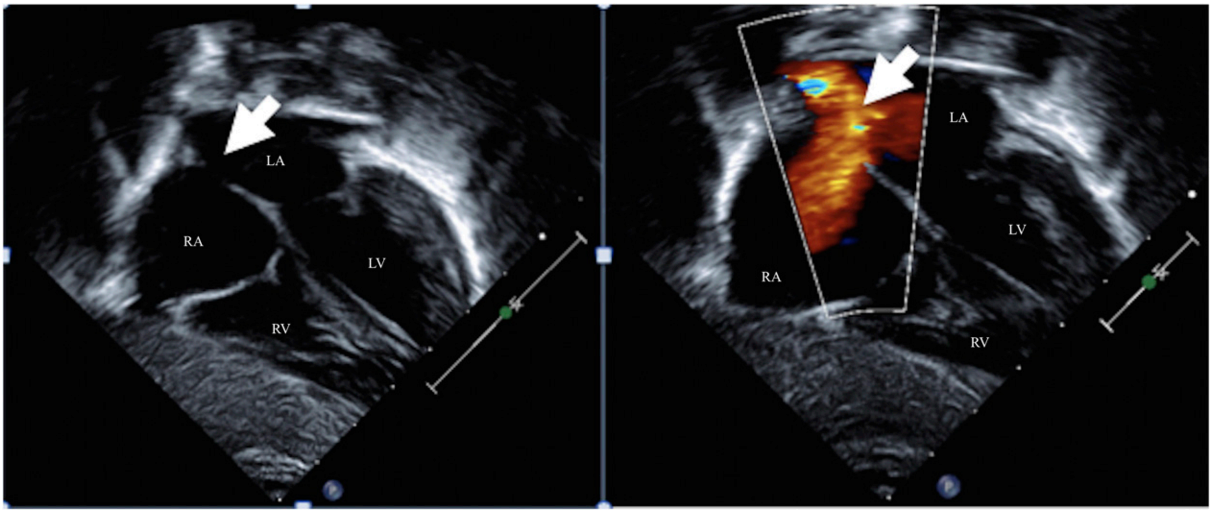

Figure 1. Subcostal echocardiogram of a secundum atrial septal defect (indicated by arrow) with and without color. LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle.

POST-TRICUSPID VALVE SHUNTS

Left-to-right shunting lesions distal to the tricuspid valve include various ventricular septal defects (VSDs; eg, perimembranous VSD and atrioventricular canal defects) and systemic to pulmonary shunts (eg, patent ductus arteriosus [PDA] and aortopulmonary window). The hemodynamic significance of a shunt depends on the size and resistance *within* the defect, and the relationship between pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR). In utero and immediately after birth, the PVR and SVR are approximately equal, producing a PVR/SVR ratio of 1:1. After a healthy newborn takes the first breath, the pulmonary vascular bed is exposed to oxygen, promoting pulmonary arteriolar relaxation and a progressive decrease in the PVR/SVR ratio. PVR reaches its nadir between 8 weeks and 6 months of age, resulting in a PVR/SVR ratio of 0.2:1 or less. Regardless of the size and resistance within a post-tricuspid valve communication, net shunting of blood will not occur until the PVR/SVR ratio has deviated significantly from 1:1 (ie, an increase in pulmonary blood flow relative to systemic blood flow cannot occur until PVR is less than SVR).

The PVR/SVR ratio effectively acts as the second in a series of 2 resistors, with the first being the communication itself. The Hagen-Poiseuille equation states that resistance to flow across a vessel is directly related to its length and inversely related to its radius to the fourth power ($R = L/r^4$). VSDs have no length and act as a static resistor in the neonate, therefore, the resistance to flow across the VSD is entirely determined by the radius or size of the defect. By comparison, a PDA has significant length and its radius is affected by both contraction of oxygen-sensitive ductal tissue and angulations within a tortuous ductus. However, the relative resistance that exists within the pulmonary and systemic vascular beds is markedly greater than that found within the defects themselves, and is subsequently the largest determinant of shunting volume and direction. These complex interactions ultimately determine whether a post-tricuspid valve shunting lesion produces a pressure and/or volume burden on the heart and lungs.

VSD shunting occurs exclusively during systole. Large nonrestrictive VSDs are associated with pulmonary arterial pressures identical to systemic arterial pressures, regardless of the PVR/SVR ratio. This is because pressure generation within a vascular bed is the product of its vascular resistance (PVR and SVR) and pulmonary (Qp) and systemic (Qs) blood flow ejected into that bed. For example, if the ratio of resistance is 1:1, there is no net shunting (Qp:Qs = 1:1), but if the PVR/SVR ratio is 0.5:1 and the Qp:Qs is 2:1, the pulmonary circulation is exposed to twice as much blood flow as is the systemic circulation.

VSDs in the setting of a low PVR/SVR ratio (ie, <0.5:1) produce a volume burden on both the lungs and left ventricle. Excess pulmonary blood flow shunted from the left ventricle combines with the right ventricular output and produces hydrostatic pressures that overwhelm oncotic forces, resulting in intra-alveolar water or pulmonary edema. This total blood volume must then return to the left atrium and ventricle, progressively dilating both chambers. Newborns with such ventricular level shunting become increasingly tachypneic, intolerant of oral feedings, and fail to thrive, producing the classic presentation of congestive heart failure. This rate of decline is reduced with smaller defects and if the PVR/SVR is closer to 1:1. Large, long-standing, unrepaired VSDs cause progressive pulmonary arteriolar vasoconstriction and PVR elevation that eventually becomes irreversible, resulting in Eisenmenger syndrome; this is exceedingly rare in the first few years of age.

Although the length of a PDA directly increases resistance, compared with a large VSD, PDAs typically produce a larger volume burden on the pulmonary vascular bed for 2 reasons. First, a newborn's ductus arteriosus is large, with a cross-sectional area equal to the descending aorta, largely counteracting the resistance effect of its length. Second, shunting occurs throughout both systole and diastole.

VENTRICULAR SEPTAL DEFECT

Incidence

VSDs are the most common form of CHD, representing 20% to 30% of isolated lesions and occurring in 1.3 to 3.9 of 1,000 live births. (12)(13) VSDs are classified as 4 types, with perimembranous VSDs being the most common. (14) Isolated VSDs are the most common CHD seen in patients with trisomy 21, 18, and 13, but only 5% to 8% of patients with an isolated VSD will have a chromosomal disorder. (13) *TBX5*, *GATA4*, and *NKX2* mutations have been associated with isolated VSDs. (13)

Diagnosis

Small, restrictive VSDs are often found incidentally with a holosystolic murmur at the left sternal border, but only after PVR has begun to fall. Because of the lack of flow acceleration and associated murmur, large defects may not become clinically evident until an infant becomes symptomatic, as described earlier. Chest radiography may show signs of pulmonary congestion and an enlarged cardiac silhouette. An ECG may show signs of left and right ventricle hypertrophy with disease progression, but are typically not diagnostic. Echocardiography is the diagnostic tool of choice (Fig 2) and additional testing is not usually indicated.

Management

Up to 45% of VSDs spontaneously close during the first year of age. (12) For those that become hemodynamically significant, surgical closure is the primary option, depending on the location of the defect and size of the child, with low morbidity and mortality rates and excellent outcomes. (12) Premature infants with VSDs are particularly challenging because their incomplete pulmonary arteriolar development produces an extremely compliant pulmonary vascular bed, resulting in an earlier onset of pulmonary overcirculation and congestive heart failure. This is further complicated in patients with chronic lung disease. Pulmonary artery banding may be considered if there are multiple defects within the ventricular septum or if the infant's size or gestational age precludes cardiopulmonary bypass. (12)

ATRIOVENTRICULAR SEPTAL DEFECT

Incidence

AVSDs comprise a wide variety of congenital heart lesions involving endocardial cushion formation. The spectrum ranges from partial defects with a primum ASD and mitral valve cleft (most common type) to a complete defect with an ASD, VSD, and single atrioventricular valve to an unbalanced AVSD with heterotaxy syndrome and single ventricle physiology. (15)(16) The incidence of AVSDs ranges from 0.24 to 0.31 per 1,000 live births or 4% to 5% of congenital heart defects and 40% of cases will be associated with trisomy 21. (16)(17) AVSD is associated with tetralogy of Fallot in 5% of cases. (16)

Diagnosis

A complete AVSD is commonly diagnosed prenatally. (16)(17) Defects with large ventricular components will present earlier in life when PVR falls, as discussed earlier. Diagnosis is made with echocardiography (Fig 3), but ECG can be a helpful screening test because it commonly shows the unique finding of a superior QRS axis between −90 and −120 degrees (Fig 4).

Management

Definitive management is surgical, with current mortality rates less than 3% when performed between 3 and 6 months of age, which increases in younger, smaller infants. (18) The concurrent diagnosis of trisomy 21 syndrome does not significantly alter morbidity or mortality rates unless surgical intervention is made significantly later than 6 months of age, because of an inherently earlier development of irreversible pulmonary vascular disease. (16)

PATENT DUCTUS ARTERIOSUS

Incidence

The PDA is a vital structure in utero, redirecting blood from the right ventricle to the lower body. After a term gestation, the PDA will usually close within 72 hours of age, but frequently this does not occur until much later in preterm infants, making it the most common lesion of prematurity. (19)(20)

Diagnosis

Patients may demonstrate a widened pulse pressure with bounding distal pulses; auscultation of the left upper sternal border will demonstrate either a continuous murmur

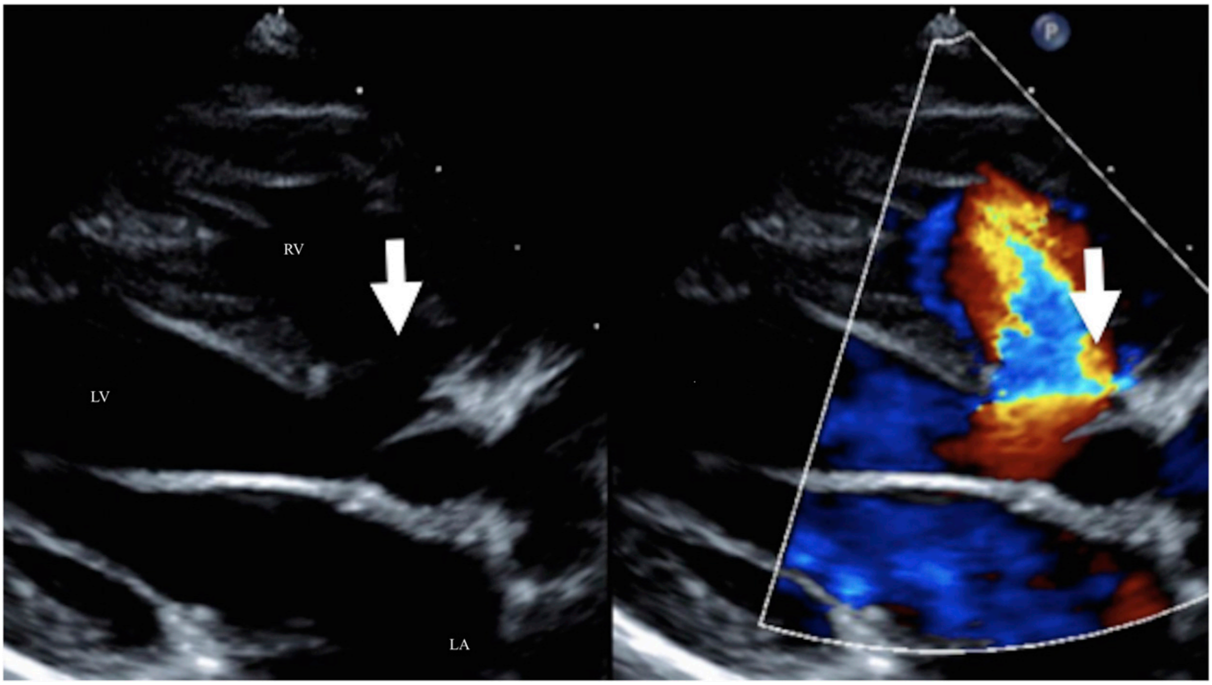

Figure 2. Echocardiogram in parasternal long axis view, with and without color, demonstrating a perimembranous ventricular septal defect (indicated by arrow). LA=left atrium; RV=right ventricle; LV=left ventricle.

produced by shunting throughout the cardiac cycle or an isolated systolic murmur either when the PVR remains high or as the ductus begins to close and diastolic flow ceases. As with other left-to-right shunts, echocardiography is the diagnostic tool of choice. Some investigators have demonstrated serum brain natriuretic peptide to be another indicator of PDAs in premature infants. (19)(21)

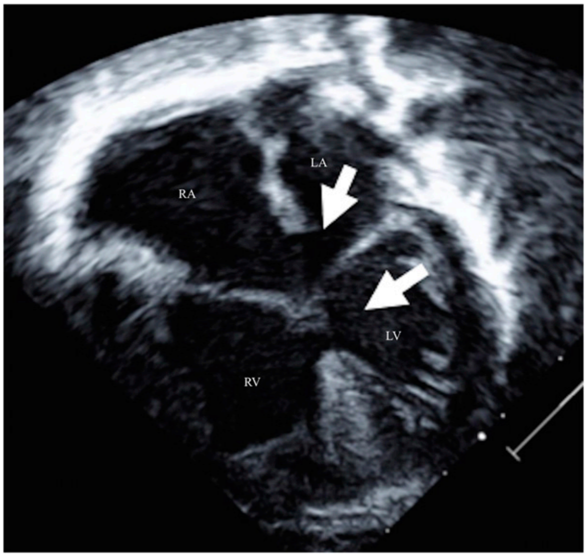

Figure 3. Apical echocardiogram of an atrioventricular septal defect showing a primum atrial septal defect (top arrow), a common atrioventricular valve, and an inlet ventricular septal defect (bottom arrow). LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle.

Management

Spontaneous PDA closure is more likely to occur in infants without respiratory distress syndrome, those born after 28 weeks' gestation (~73%), and those born with birthweights greater than 1,000 g (~ 94%). (19)(22) When closure does not occur, it is reasonable to consider intervening in the setting of chronic renal insufficiency, feeding intolerance, hemodynamic instability, or inability to separate from supplemental respiratory support. Nonsteroidal anti-inflammatory agents such as indomethacin and ibuprofen are commonly considered first-line therapy. However, their mechanism of action (cyclooxygenase inhibition with downstream inhibition of prostaglandin formation) (23)(24) also carries a significant risk of acute renal injury, intracranial hemorrhage, and spontaneous intestinal perforation. This challenge has prompted investigation into alternative medical interventions such as intravenous acetaminophen. (24)

Surgical ligation is another option, but is associated with risks of vocal cord or diaphragm paresis, scoliosis, or accidental ligation of the pulmonary artery or aorta. (25) Percutaneous device occlusion is yet another option, but higher rates of arterial injury and device embolization are reported in infants who weigh less than 4 kg. (25) Considering the complicated risk-benefit profile associated with these options, the decision

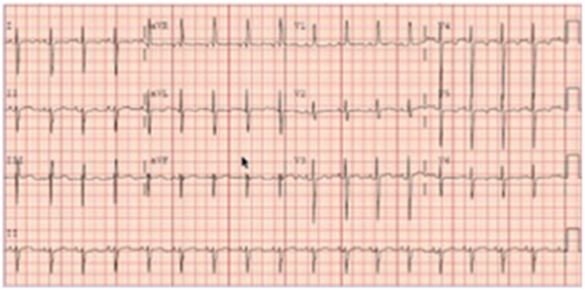

Figure 4. Electrocardiogram of a patient with an atrioventricular septal defect demonstrating a superior QRS axis (predominantly negative QRS waveform in lead I and aVF) consistent with an endocardial cushion defect.

to intervene in an infant with a PDA should not follow a protocol, but instead be individualized for each patient.

Premature Infants

Some data suggest that the premature ductus arteriosus is less sensitive to the vasoconstrictive properties of oxygen and more sensitive to the vasodilatory effects of endogenous prostaglandin E_2, (26) resulting in the higher prevalence of ductal patency in this population. As with VSDs in the premature infant, PDAs can be especially challenging because they contribute to heart failure, bronchopulmonary dysplasia, necrotizing enterocolitis, renal insufficiency, cerebral palsy, and prolonged need for ventilator support. (19)

AORTOPULMONARY WINDOW

Aortopulmonary windows are a rare (0.2%–0.6% of CHD) systemic to pulmonary communication associated with severe pulmonary overcirculation, heart failure, and respiratory failure. (27) This defect occurs during embryonic septation of the truncus arteriosus in which the 2 vessels have a region devoid of intervening tissue. Without any interposing resistor such as a semilunar valve or length of ductus arteriosus, there is no functional separation between the systemic and pulmonary vascular beds and patients become symptomatic at very young ages. Physical examination findings are typically indistinguishable from those of a large PDA. Echocardiographic diagnosis can be challenging but should be suspected in patients with a clinical picture of heart failure without a PDA or VSD. Surgical patch septation is the definitive intervention.

CONCLUSION

Left-to-right shunting lesions should be physiologically and anatomically subcategorized into pre- and post-tricuspid valve. Pre-tricuspid valve lesions include ASDs in which shunting is determined by defect size and differences in ventricular compliance. These lesions produce right heart enlargement and are usually asymptomatic throughout infancy. Post-tricuspid valve lesions include VSDs, AVSDs, PDAs, and aortopulmonary windows, in which shunting is determined largely by the relationship between the systemic and pulmonary vascular resistances but also by the resistance inherent in the interposing defect. Initially, these lesions produce a volume burden on the lungs and left ventricle, and can lead to progressive respiratory failure, heart failure, and failure to thrive. Untreated, any of these lesions can progressively result in Eisenmenger syndrome, which is associated with a significantly worse prognosis. Premature infants and those with chronic lung disease are particularly sensitive to left-to-right shunting lesions and should be considered for early medical or surgical intervention.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the anatomy and pathophysiology (including genetics) of a neonate with a left-to-right shunt lesion.
- Recognize the clinical features of a neonate with a left-to-right shunt lesion.
- Recognize the laboratory, imaging, and other diagnostic features of a neonate with a left-to-right shunt lesion.
- Formulate a differential diagnosis for a neonate with a left-to-right shunt lesion.
- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for a neonate with a left-to-right shunt lesion.

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1. A newborn with a murmur undergoes echocardiography and is noted to have an atrial septal defect (ASD). It is reported that ASDs occur in approximately 1 in 1,500 children and account for 6% to 10% of all cardiac anomalies. Which of the following subtypes constitutes the most common type of ASD?
    A. Ostium primum ASD.
    B. Sinus venosus type ASD.
    C. Ostium secundum ASD.
    D. Coronary sinus ASD.
    E. Mixed ASD.
2. In utero and immediately after birth, the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR) is approximately 1:1. With exposure of the pulmonary vascular bed to oxygen, the PVR/SVR ratio progressively decreases. When does the PVR nadir occur in a healthy neonate?
    A. At 1 week of age.
    B. Between 2 and 4 weeks of age.
    C. Between 4 and 8 weeks of age.
    D. Between 8 weeks and 6 months of age.
    E. Between 6 months and 12 months of age.
3. A male term newborn is noted at 1 day of age to have a holosystolic murmur. Echocardiography reveals a ventricular septal defect (VSD). VSDs are the most common form of congenital heart disease, representing 20% to 30% of isolated lesions and occurring in 1.3 to 3.9 of 1,000 live births. Which of the following statements is FALSE regarding the physiology of VSDs?
    A. VSDs in the setting of a low PVR/SVR ratio (ie, <0.5:1) produce a pressure burden on both the lungs and left ventricle.
    B. Pulmonary edema is the result of excess pulmonary blood flow with resultant increased hydrostatic pressures.
    C. The classic presentation of a large hemodynamically significant VSD includes tachypnea, intolerance of oral feeds, and failure to thrive.
    D. If untreated, excess pulmonary blood flow can lead to progressive pulmonary arteriolar vasoconstriction and irreversible PVR elevation (Eisenmenger syndrome).
    E. Due to the lack of flow acceleration and associated murmur, large defects may not become clinically evident until an infant becomes symptomatic.
4. A female term newborn has features of trisomy 21 and part of the evaluation includes echocardiography, which reveals an atrioventricular septal defect (AVSD). AVSDs account for 4% to 5% of congenital heart defects and 40% of cases are associated with trisomy 21. Which of the following electrocardiographic (ECG) findings is unique to AVSDs?
    A. Presence of right ventricular hypertrophy and right axis deviation.
    B. Presence of a superior QRS axis between –90 and –120 degrees.
    C. Presence of peaked, large amplitude p waves in lead II.
    D. Presence of left ventricular hypertrophy with left axis deviation.
    E. Presence of prolonged PR interval.
5. An infant born at 34 weeks' gestational age has respiratory distress and is placed on continuous positive airway pressure. Chest radiography shows a large cardiac shadow and cardiac murmur. The patient continues to have respiratory distress and oxygen requirement at 2 days of age and echocardiography is performed. Patent ductus arteriosus (PDA) is present, but otherwise the cardiac anatomy is normal. In full-term infants, the PDA usually closes within 72 hours of age. Which of the following statements is also correct regarding PDAs?

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A. As with ventricular septal defects, shunting occurs exclusively in systole.
B. The premature ductus arteriosus is less sensitive to the vasodilatory effects of endogenous prostaglandin $E_{2.}$
C. The PDA is more likely to spontaneously close in infants without respiratory distress syndrome.
D. The PDA spontaneously closes in approximately 75% of preterm infants with a birthweight above 1,000 g.
E. The rate of complications associated with percutaneous device occlusion of the PDA is similar in older children and neonates weighing more than 2,500 g.

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Right and Left Ventricular Outflow Tract Obstructive Lesions

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Education Gap

It is important to understand the pathophysiology, disease progression, and initial management of left and right obstructive lesions and how they pertain to appropriate care for infants in the NICU.

Abstract

Obstructive cardiac lesions are a common type of congenital heart disease ranging in severity from asymptomatic, mild valvular stenosis to valvar atresia with congestive heart failure and cyanosis. Understanding the pathophysiology and initial management of right and left ventricular outflow tract obstruction is imperative to minimize morbidity and mortality in term and preterm infants.

Objectives

After completing this article, readers should be able to:

1. Explain the pathophysiology, initial presentation, and management of left and right obstructive lesions in congenital heart disease.
2. Identify the various forms of left and right obstructive lesions.
3. Recognize how management of these lesions differs between term and preterm infants.

INTRODUCTION

Left ventricular outflow tract (LVOT) obstructive lesions comprise a spectrum of cardiac anomalies ranging in severity from mild, asymptomatic valve stenosis to complete vessel atresia (a form of cyanotic congenital heart disease [CHD], which will not be discussed in this review). Obstruction can occur at any level distal to the ventricular cavity including the outflow tract (a portion of the ventricle between its body and semilunar valve), semilunar valve (ie, aortic or pulmonary valve), supravalvar region, or more distal vessel narrowing (eg, pulmonary artery stenosis or coarctation of the aorta). The dominant physiologic consequence of these lesions is an increase in ventricular afterload, imposing an additional burden against which the ventricle must contract to eject blood. Patient presentation is

AUTHOR DISCLOSURE Drs Colombo and McCulloch have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CHD	congenital heart disease
LVOT	left ventricular outflow tract
RVOT	right ventricular outflow tract

largely dependent on the ventricular response to both obstruction severity and rate of development.

The Laplace law $\{\sigma = (Pxr)/h\}$ describes the process in which ventricular wall stress (myocardial force generation) is directly related to pressure generation (product of cardiac output and vascular resistance) and ventricular dimension (radius) and indirectly related to myocardial mass. Thus, the healthy myocardium will undergo compensatory hyperplasia (infants) (1) and/or hypertrophy (infants and older children/adults) (1) to offset chronically increased afterload and/or ventricular dilation. If wall stress increases suddenly, however, hypertrophy cannot occur and systolic failure ensues, resulting in low cardiac output and end organ failure. Conversely, while progressive obstruction allows for compensatory increases in ventricular mass with maintenance of wall stress and systolic function, significant thickening reduces ventricular compliance, resulting in increased end diastolic (filling) pressures, diastolic dysfunction, and secondary venous congestion.

In general, obstruction severity and location dictates clinical symptoms and presentation. This review will differentiate obstructive lesions comparing the pulmonary and systemic circulations by means of clinical symptoms, outcomes, follow-up, and management.

OBSTRUCTIVE LESIONS OF THE LEFT VENTRICLE/SYSTEMIC CIRCULATION

Obstructive lesions of the left ventricle/systemic circulation range in pathology from simple bicuspid aortic valves (Figs 1A and 1B) to hypoplastic left heart syndrome and are associated with a strong genetic predisposition. First-degree relatives have a 10% increased risk of inheriting an obstructive lesion and the link is stronger if the mother is affected. (2)

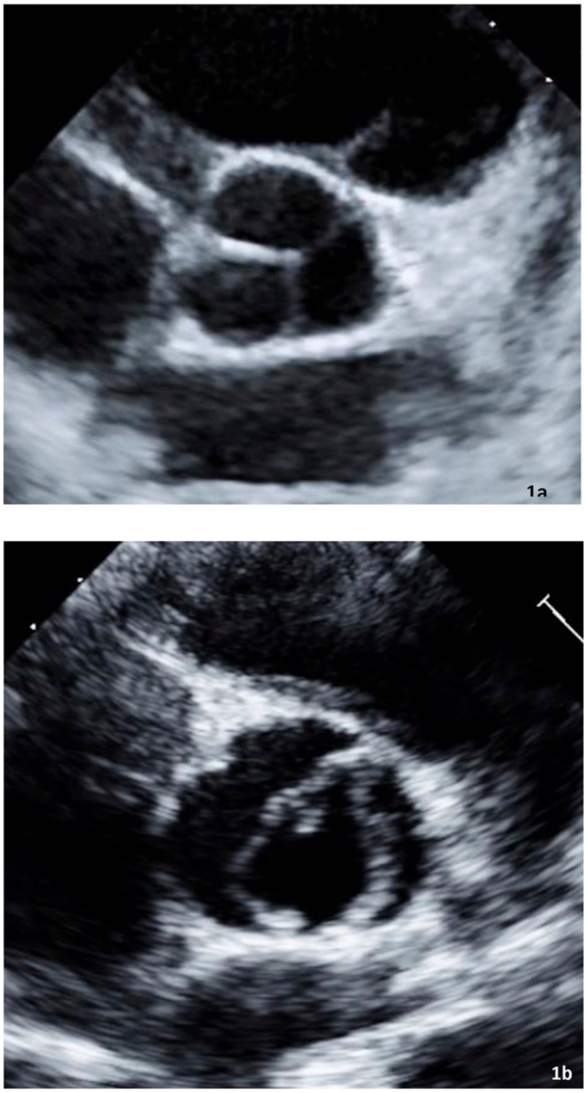

Figure 1. A. Echocardiogram of a normal trileaflet closed during diastole. B. Echocardiogram of a bicuspid aortic valve during systole demonstrating fusion of the right and noncoronary artery cusp. This is 1 of 2 variants in bicuspid aortic valve. Left and right coronary cusp fusion also occurs.

Aortic Valve Stenosis

Congenital aortic valve stenosis occurs in 0.2 to 0.5 per 1,000 live births, has a male predominance, (3) is associated with other congenital heart defects in 20% of cases, (4) and is the most common form of left ventricular obstructive lesion. Affected valves may demonstrate fusion of 1 or more commissures, limiting leaflet excursion and functional valve orifice. When combined with rapid somatic growth in the neonatal period and systemic vascular resistance, such infants may readily overwhelm available left ventricular cardiac output. If stenosis progresses more rapidly than compensatory hypertrophy and hyperplasia, left ventricular failure, cardiogenic shock and multisystem organ failure ensue and are associated with high morbidity and mortality rates. (5)(6) Because of these potential outcomes, infants with aortic valve stenosis should receive frequent reassessment because an intervention is commonly required in the first year of age. (7)

In an infant with aortic valve stenosis, the physical examination is characterized by a harsh, systolic ejection murmur best auscultated at the right upper sternal border. If accompanied by poor left ventricular function, however, as in critical aortic stenosis, the murmur will be softer and accompanied by poor or absent peripheral pulses. Electrocardiography will demonstrate large left ventricular voltages and potentially a strain pattern (Fig 2) but ultimately, echocardiography is used to confirm the diagnosis. Echocardiography can assess left ventricular function and associated defects and

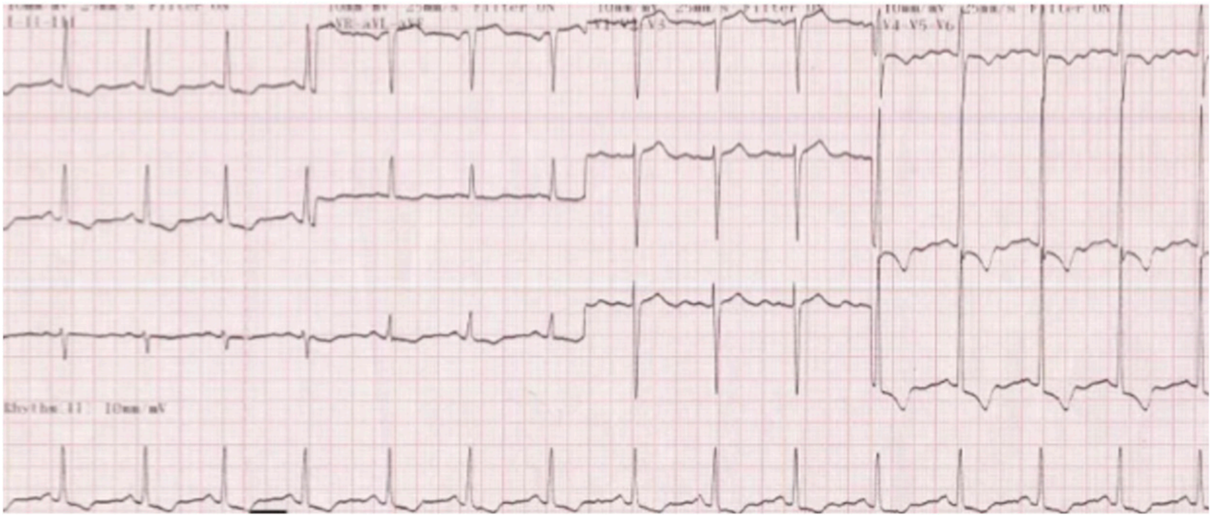

Figure 2. Electrocardiogram demonstrating left ventricular hypertrophy with R waves greater than 25 mm in V6 and strain pattern with upright T waves in V1 with abnormal progression and inversion in V3 to V6.

evaluate aortic stenosis gradient; values greater than 60 mm Hg are typically considered an indication for intervention. (8) However, the actual gradient becomes irrelevant when associated with left ventricular dysfunction, in which case intervention is indicated imminently.

Critical aortic valve stenosis in a newborn should prompt consideration for initiation of a prostaglandin E_2 infusion to either maintain or reestablish ductal patency and allow the right ventricle to augment systemic cardiac output. Once an infant is stabilized, management options include cardiac catheterization with balloon aortic valvuloplasty or surgical valvotomy. Balloon valvuloplasty obviates cardiopulmonary bypass, which can be poorly tolerated in the setting of ventricular dysfunction, but is associated with a higher incidence of clinically significant aortic valve insufficiency. (6)(9) Conversely, the need for cardiopulmonary bypass may be offset by less insufficiency and longer freedom from valve replacement after surgical valvotomy. (10) Each patient should receive individual consideration.

Though a causal link has not been identified, severe aortic valve stenosis identified early in gestation has been suspected to progress to hypoplastic left heart syndrome and endocardial fibroelastosis in some fetuses. (6) In utero balloon aortic valvuloplasty has been successfully performed with the intention to prevent this progression to single ventricle physiology and anatomy. Although some patients receive significant improvements, such interventions carry significant morbidity and mortality. (6)

Subaortic Valve Stenosis

Subaortic valve obstruction is typically secondary to a discrete membrane or tunnel-like obstruction (30% of congenital LVOT obstruction). (2)(11) Approximately 45% to 65% of affected patients will have other forms of CHD and 50% will have associated aortic valve disease. (11) These lesions are less likely to present in the newborn period and may actually result from chronic turbulent flow rather than a true congenital lesion, with progressive obstruction correlating with age. (2)(11)(12) Physical examination and electrocardiographic findings in infants with subaortic valve stenosis are very similar to those of aortic valve stenosis, and echocardiography is used to confirm the diagnosis. Recurrence rates after surgical subaortic membrane resection are reported in up to 40%, and increase with tunnel-like obstructions, younger age at onset, or associated CHD. (11)(12) Surgical resection is the treatment of choice for discrete membranes, but tunnel-like obstructions can require LVOT reconstruction, which is not typically feasible in small infants.

Supravalvar Valve Stenosis

Supravalvar aortic stenosis is the rarest form of LVOT obstruction and is characterized by narrowing at the sinotubular junction, which can extend into the ascending aorta, and rarely, the aortic arch (Fig 3). Aortic valve disease is also present in 50% of affected patients and accompanying subvalvar stenosis in 16% of cases. (2) Any patient diagnosed with supravalvar aortic stenosis should be evaluated for the *Elastin* gene mutation associated with Williams-Beuren syndrome because this mutation also causes stenosis of the branch pulmonary arteries and coronary ostia. While the former can produce severe right ventricular hypertrophy and failure, the latter significantly increases the risk of myocardial ischemia and death with anesthesia or

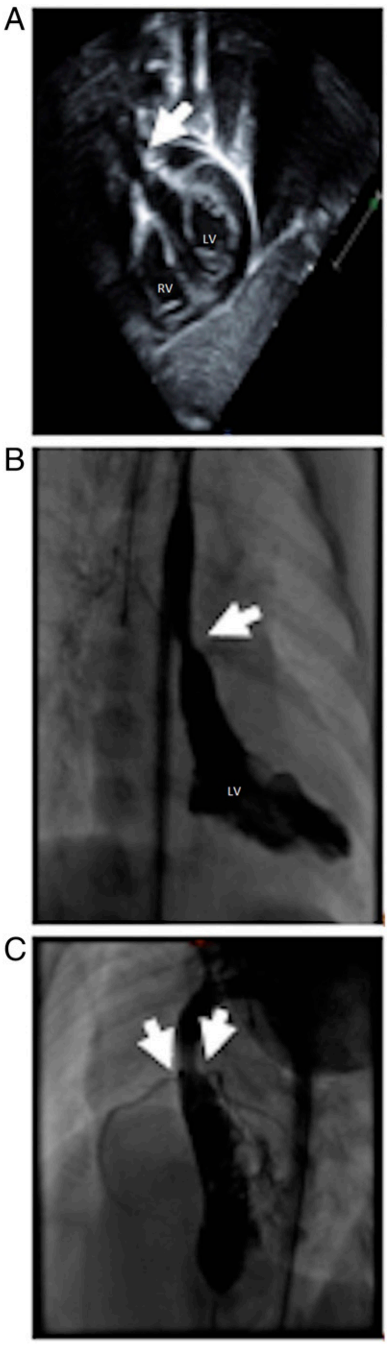

Figure 3. A. Subcostal echocardiographic view in a patient with Williams syndrome and supravalvar aortic stenosis (arrow) as demonstrated by the classic hourglass finding. B. An angiogram of the same patient with injection into the left ventricle also demonstrates supravalvar aortic stenosis (arrow). C. Lateral view of the same angiogram demonstrating the proximal coronary artery stenosis bilaterally (arrows). LV=left ventricle; RV=right ventricle.

any other source of systemic hypotension. (13) Physical examination findings may be indiscernible from those of valvar or subvalvar aortic stenosis unless the pulmonary arterial bed is also involved. Echocardiography is ultimately used to confirm the diagnosis but electrocardiography may provide additional evidence of myocardial strain or ischemia in severely affected patients. Management involves surgical resection and augmentation of the narrowed region and affected coronary ostia.

Aortic Coarctation

Coarctation of the aorta is a distal LVOT obstruction, occurring in 0.4 of 1,000 live births and comprising 6% to 8% of all CHD. (2)(3)(14) It can occur as a discrete narrowing or as diffuse hypoplasia of the entire aortic arch (Fig 4). Although discrete coarctation typically occurs at the insertion of the patent ductus arteriosus into the descending aorta, lower thoracic and abdominal coarctation does occur. (15) Coarctation is often associated with other forms of congenital heart defects, including ventricular septal defects (15) and bicuspid valve in 22% to 75% of cases. (2)(3) A male preponderance has been noted, but female patients should have special consideration because coarctation is common in Turner syndrome. (2)(14)

Once coarctation has developed, classic physical examination findings include a systolic ejection murmur at the left upper sternal border with radiation to the back, and diminished lower extremity pulses. As with critical aortic valve stenosis, however, when coarctation is severe and produces left ventricular failure, both the murmur and pulses may be markedly diminished. Electrocardiography may show left ventricular hypertrophy and a strain pattern but echocardiography is used to confirm the diagnosis.

Neonatal repair is indicated in the setting of hemodynamic compromise or systolic blood pressure gradients higher than 20 mm Hg between the upper and lower extremities. (15) Surgical outcomes are typically excellent,

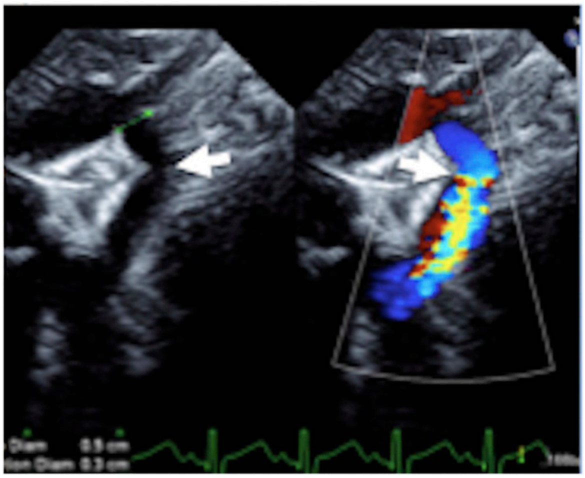

Figure 4. Two-dimensional image of the suprasternal notch of a discrete coarctation of the aorta (arrow) showing discrete narrowing at the aortic isthmus. When color is added, flow acceleration is seen across the narrowed area.

with low morbidity and mortality for infants after extended end-to-end anastomosis (16); however, recoarctation occurs in 4% to 13% (15) and left recurrent laryngeal nerve injury occurs in 48%, causing vocal cord dysfunction. (17)

Some studies have linked low birthweight (<2 kg) and prematurity with significantly increased rates of recoarctation and mortality. (18) Conversely, others have found no such association and instead, correlate mortality to preoperative clinical condition and combination repairs with other complex CHD. (19)

Hypertrophic Obstructive Cardiomyopathy

Hypertrophic obstructive cardiomyopathy exists in 2 distinct neonatal forms: genetic hypertrophic cardiomyopathy and diabetic cardiomyopathy. Diabetic cardiomyopathy occurs in infants of diabetic mothers and is the consequence of poorly controlled maternal glucose and fetal hyperinsulinemia, especially during the third trimester. It occurs in 30% of such infants, with 12.1% becoming symptomatic. (20) After birth, the infant is separated from the hyperglycemic maternal serum, which allows for hypertrophic regression over the first few weeks of age. (20) Management is seldom required during this period except when associated with persistent fetal circulation and systemic hypoperfusion. Such patients may require low-dose β-blockade and nonchronotropic afterload agents to mitigate the hypercontractile, left ventricular cavity obliteration that precludes ventricular relaxation, diastolic filling, and normal transition of the pulmonary vascular bed.

By comparison, congenital hypertrophic cardiomyopathies are characterized by myofiber disarray and severe hypertrophy, with a higher incidence of myocardial ischemia, arrhythmia, and death. (21) When diagnosed in infancy, congenital hypertrophic cardiomyopathy is associated with a 21% incidence of mortality or need for heart transplantation at age 2 years, which increases to 57% if the diagnosis is associated with an inborn error of metabolism. (22) Conversely, infants with idiopathic hypertrophic cardiomyopathy surviving past 1 year of age have annual mortality rates similar to those of the general population. The mainstay of hypertrophic cardiomyopathy management is preventing dehydration and systemic hypotension and achieving lower heart rates to allow time for ventricle filling and preload.

RIGHT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Pulmonary valve stenosis composes up to 90% of all right ventricular outflow tract (RVOT) obstruction, affecting 5.5 per 10,000 live births and almost 9% of all CHD cases (Fig 5). (23)(24)(25) As with aortic valve stenosis, pulmonary valve stenosis is characterized by thickened leaflets with intercommissural fusion, narrowing the effective valve orifice (Fig 6). By comparison, however, pulmonary valve stenosis–induced right ventricular failure is far less common than left ventricular failure associated with aortic stenosis. This is because of the intrinsic hypertrophy of the neonatal right ventricle, which is conditioned by a gestation's worth of high afterload from elevated pulmonary vascular resistance, and its rapid decline in postnatal life.

Semilunar (aortic and pulmonary) valve formation occurs through complex signaling pathways during embryologic development. Disruption in these pathways causes mutations seen in Noonan and LEOPARD syndromes, due to *PTPN11* gene disruption and *SHP-2* gene anomalies. (26) The 22q11 deletion is commonly seen in patients with tetralogy of Fallot, a constellation of cardiac pathology consisting of pulmonary valve stenosis, right ventricular hypertrophy, a ventricular septal defect, and overriding aorta, often leading to cyanosis. Alagille syndrome (*JAG1* gene mutation), Williams-Beuren syndrome, congenital rubella, and Ehler-Danlos syndrome are several other disorders associated with RVOT obstruction, specifically due to peripheral pulmonary artery stenosis (Fig 7). (27)

Pulmonary valve stenosis is often diagnosed prenatally with fetal echocardiography. (12) If mild to moderate stenosis is present during the third trimester of pregnancy, two-thirds of these infants will develop severe pulmonary valve stenosis or atresia due to poor annular growth; single ventricle palliation may be required. (6)(28) If stenosis occurs later in fetal development, right ventricular and tricuspid valve growth is typically preserved and most of these infants can undergo biventricular repair. (6)(28)

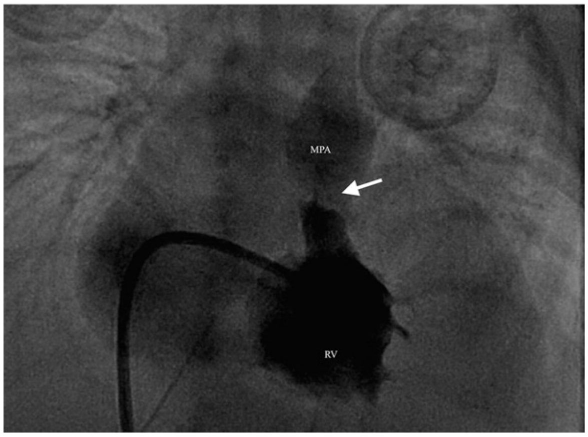

Figure 5. Angiographic representation of critical pulmonary valve stenosis. Here, the catheter is across the tricuspid valve with contrast injection into the small right ventricle. The arrow indicates the location of the pulmonary valve. MPA=main pulmonary artery; RV=right ventricle.

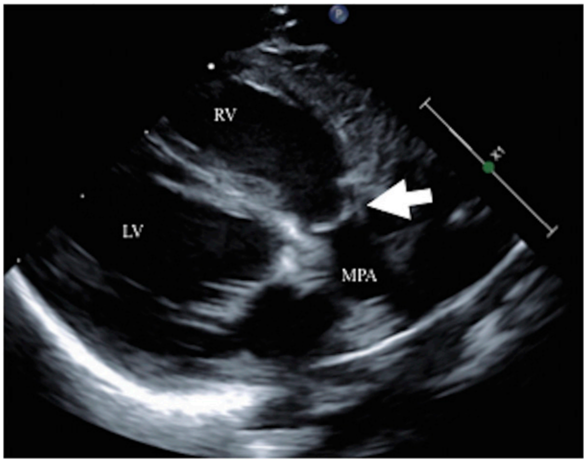

Figure 6. Parasternal long-axis view on a transthoracic echocardiogram showing a thickened doming and dysplastic pulmonary valve (arrow). LV=left ventricle; MPA=main pulmonary artery; RV=right ventricle.

Natural history studies suggest that most pulmonary valve stenosis, is mild with little to no disease progression (29)(30); however, rare patients can progress unexpectedly, mandating ongoing follow-up during the first 1 or 2 years of age. (30) Physical examination will demonstrate a classic systolic ejection murmur at the left sternal border, and in severe cases, can be associated with systemic desaturations. In contrast to aortic valve stenosis, the murmur across a stenotic pulmonary valve becomes increasingly louder over the initial few days after birth as pulmonary vascular resistance falls, producing a pressure gradient and the flow acceleration needed to create a murmur; this explains why some patients are not identified in the first 48 hours of age. In the affected newborn, electrocardiography will show typical right ventricular hypertrophy and a right QRS axis, but may not make a transition toward a left QRS axis and normal right ventricular forces over the first several months of age in patients with significant stenosis. As with most neonatal CHD, however, echocardiography remains the diagnostic study of choice.

Benign, physiologic peripheral pulmonary artery stenosis is a common finding in many neonates making a transition from fetal circulation. Such patients have a classic systolic ejection murmur that radiates to the axillae, but residual narrowing is rarely present past 9 months of age, obviating any intervention.

Critical pulmonary valve stenosis is defined as severe narrowing precluding the right ventricle from ejecting an entire cardiac output through the pulmonary valve and instead, requiring a patent ductus arteriosus to ensure adequate pulmonary blood flow; as with critical aortic valve stenosis, consideration should be given to initiating a prostaglandin E_2 infusion in affected newborns. When intervention is indicated, cardiac catheterization with balloon valvuloplasty (Fig 8) is the treatment of choice. Mild to moderate forms of pulmonary valve stenosis have excellent results after a single valvuloplasty, but critical pulmonary valve stenosis may be complicated by residual obstruction and require serial catheterizations or even surgical correction. (31) Pulmonary valve insufficiency is common after valvuloplasty as valve leaflets may no longer coapt appropriately. Insufficiency is initially well tolerated but with time, right ventricular dilation and dysfunction may occur, necessitating pulmonary valve replacement. (32)(33)

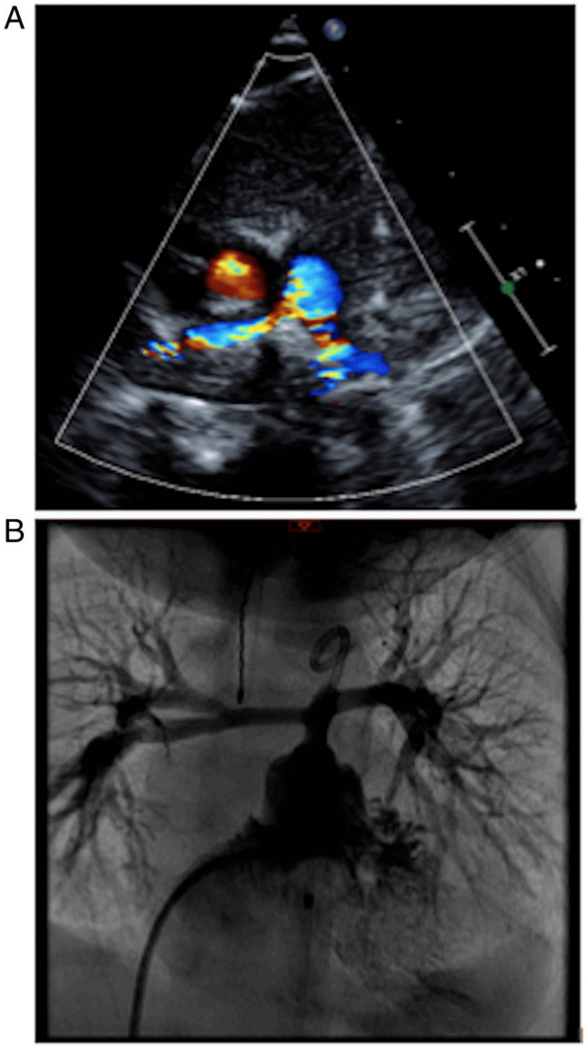

Figure 7. A. Parasternal short-axis view on echocardiogram of a patient with Williams syndrome and severe bilateral branch pulmonary artery stenosis. B. Angiogram of the same patient.

CONCLUSION

Obstructions of the LVOT and RVOT comprise a constellation of afterload-inducing lesions, with ventricular consequences

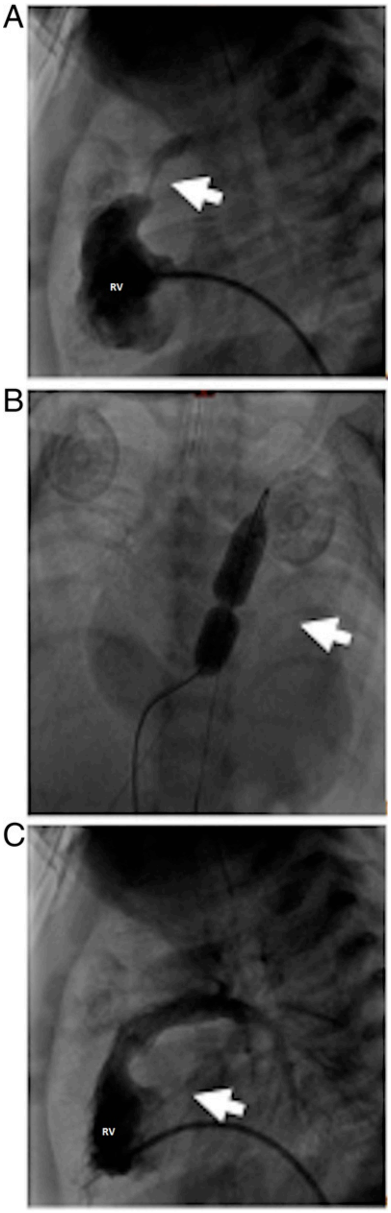

Figure 8. Angiogram of cardiac catheterization in a patient with critical pulmonary valve stenosis. A. Stenosis before balloon valvuloplasty (arrow). B. During balloon inflation, demonstrating narrowed region on balloon (arrow) before valve leaflets tear open. C. Pulmonary valve after the procedure with improved annular size (arrow). RV=right ventricle.

ranging from hypertrophy to diastolic dysfunction to decreased cavity size and even heart failure in those with severe disease. Fortunately, most forms of outflow tract obstruction are mild and will not require intervention in the neonatal period. Disease progression is more common in LVOT obstruction and warrants close monitoring. Diagnosis is achieved with echocardiography, but cardiac catheterization plays a critical role in providing hemodynamic data and initial treatment in severe aortic and pulmonary valvular obstruction. Management data in premature infants are limited and conflicting, and case-by-case discussions among the pediatric cardiology team are warranted.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for a neonate with a left-sided cardiac obstructive lesion.
- Know the anatomy and pathophysiology, including genetics, of a neonate with a left-sided cardiac obstructive lesion.
- Recognize the clinical features of a neonate with a left-sided cardiac obstructive lesion.
- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for a neonate with a right-sided cardiac lesion.
- Know the anatomy and pathophysiology (including genetics) of a neonate with a right-sided cardiac lesion.
- Recognize the clinical features of a neonate with a right-sided cardiac lesion.

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1. A female term newborn infant is noted to have a systolic ejection murmur at 6 hours of age. She is subsequently evaluated, and echocardiography performed at 10 hours of age reveals critical aortic valve stenosis. Up to that point, she had been cared for in the mother's postpartum room. Which of the following next steps would be most appropriate?
   - A. Admit to the NICU for further monitoring and consideration of initiation of prostaglandin E_2 infusion.
   - B. Admit to NICU for intubation and surfactant administration to improve pulmonary compliance.
   - C. Begin antibiotic prophylaxis for potential immune deficiency.
   - D. Begin diuretic therapy to reduce afterload.
   - E. The infant can stay in the mother's room but vital signs should be obtained at least every 3 hours until discharge from the hospital.
2. A male newborn infant is diagnosed with supravalvar valve stenosis. For which of the following conditions would it be appropriate to have further evaluation?
   - A. β-ketothiolase deficiency.
   - B. Congenital Zika virus infection.
   - C. Maternal use of phenobarbital.
   - D. Prader-Willi syndrome (chromosome 15 abnormality).
   - E. Williams-Beuren syndrome (elastin gene mutation).
3. A 12-day-old male infant presents with symptoms of poor feeding, pallor, and lethargy. A diagnostic evaluation reveals that he has coarctation of the aorta. Which of the following statements about this condition is correct?
   - A. Bicuspid valve is found in 80% to 90% of cases and 100% of cases when the coarctation presents as diffuse hypoplasia of the entire aortic arch.
   - B. It is commonly associated with Turner syndrome.
   - C. It occurs in 3.5 to 5 of 1,000 live births.
   - D. The most common location of the coarctation is the abdominal aorta.
   - E. There is a female preponderance.
4. A male infant born to a mother who had poorly controlled gestational diabetes during pregnancy is admitted to the NICU with hypoglycemia. He is noted to have a murmur, and echocardiography reveals hypertrophic obstructive cardiomyopathy. In contrast to congenital or genetic hypertrophic cardiomyopathy, what are the typical findings in diabetic cardiomyopathy seen in newborns?
   - A. It is characterized by higher incidence of myocardial ischemia.
   - B. It is characterized by myofiber disarray and more severe hypertrophy both macroscopically and at the cellular level.
   - C. It is more likely to lead to a need for cardiac transplantation.
   - D. It is often characterized by regression over the first few weeks of age.
   - E. It is usually associated with an inborn error of metabolism.
5. A pregnant woman undergoes fetal echocardiography, and the fetus is noted to have pulmonary valve stenosis. Delivery occurs at 39 weeks by cesarean section due to breech presentation. The infant is admitted to the NICU for further evaluation. Which of the following statements regarding this condition is correct?

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A. For infants who develop severe stenosis or atresia due to poor annular growth, single ventricle palliation may be required.
B. Pulmonary valve stenosis is the rarest type of right ventricular outflow obstruction in neonates.
C. Right ventricular failure caused by pulmonary valve stenosis is much more common than left ventricular failure associated with aortic stenosis.
D. The most common genetic condition associated with pulmonary valve stenosis is Duchenne muscular dystrophy.
E. The most common physical examination finding is a holosystolic murmur with splitting of both S1 and S2.

Right and Left Ventricular Outflow Tract Obstructive Lesions

Jamie N. Colombo and Michael A. McCulloch

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Diagnosis and Management of Patent Ductus Arteriosus

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Education Gaps

1. It is important to recognize the risks for symptomatic patent ductus arteriosus. Infants born weighing more than 1,000 g or at more than 28 weeks' gestation generally do not require pharmacologic or surgical intervention for patent ductus arteriosus.
2. Criteria that define patent ductus arteriosus pathophysiology need to be identified. Size of the ductus arteriosus alone is inadequate as a determinant when deciding whether to intervene pharmacologically or surgically. Criteria such as gestational age, postnatal age, and markers of hemodynamic significance, including degree of respiratory support, presence of oliguria, and other echocardiographic indicators, should be considered.

Abstract

Preterm infants are at increased risk for patent ductus arteriosus (PDA). Prolonged exposure to PDA may be deleterious and has been associated with neonatal morbidity and mortality. Although the molecular mechanisms underlying regulation of postnatal ductus arteriosus closure are not fully understood, clinical experience and research trials have informed recent changes in PDA management strategies and refocused treatment strategies on smaller subsets of infants who require intervention. This review examines current diagnostic and management approaches to PDA in preterm neonates.

Objectives

After completing this article, readers should be able to:

1. Explain the efficacy and associated side effects of the 3 pharmacologic agents (acetaminophen, ibuprofen, and indomethacin) used to treat a hemodynamically significant patent ductus arteriosus (PDA).
2. Identify clinical signs of a hemodynamically significant PDA.
3. Identify known risk factors for PDA in the preterm population.
4. Describe the characteristic echocardiographic features associated with a PDA and their sensitivity and specificity.

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ABBREVIATIONS

BNP	B-type natriuretic peptide
CLD	chronic lung disease
IVH	intraventricular hemorrhage
LA/Ao	left atrium to aortic ratio
LVO/SVC	left ventricular output to superior vena cava flow ratio
NEC	necrotizing enterocolitis
NSAIDs	nonsteroidal anti-inflammatory drugs
NT-proBNP	N (amino)-terminal prohormone of B-type natriuretic peptide
PDA	patent ductus arteriosus

INTRODUCTION

The ductus arteriosus is a central vascular shunt connecting the pulmonary artery to the aorta, allowing oxygenated blood from the placenta to bypass the uninflated fetal lungs and enter the systemic circulation. Rapid closure of the ductus arteriosus after birth is essential for vascular transition to the mature, divided pattern of arteriovenous circulation. Failure of ductus arteriosus closure, termed *patent ductus arteriosus* (PDA), is primarily an affliction of prematurity, with the ductus remaining open at 7 days of age in up to 64% of infants born at 27 to 28 weeks' gestation and 87% of infants born at 24 weeks. (1) There has been a shift in presentation and treatment of infants with PDA over the past 30 years. (2)(3) Before the use of antenatal corticosteroids, PDA was frequently found in premature infants of all gestational ages and was associated with respiratory distress syndrome. Treatment with indomethacin was standard, and studies evaluated the benefits of early (or even prophylactic) PDA ligation. (4)

With advances in ventilation strategies, use of antenatal corticosteroids and exogenous surfactant, and increased willingness to wait for spontaneous ductus arteriosus closure, today's more mature preterm infants rarely require intervention for a ductus arteriosus. (5) Instead, PDA management is now focused on the most premature infants, in whom the ductus can be resistant to pharmacologic treatment. This review discusses the evolving indications for treatment of a PDA and the various treatment options available.

RISK FACTORS

The incidence of PDA is inversely associated with the degree of prematurity. Other factors associated with an increased risk of PDA in the premature infant include respiratory distress syndrome, high volume of intravenous fluids (>170 mL/kg per day) in the first week, sepsis, prolonged rupture of membranes, furosemide, male sex, and other contributors. (6) Evidence also shows that aminoglycoside antibiotics and certain antacids, frequently used in neonates, paradoxically increase the risk of a PDA. (7) Antenatal corticosteroids (8) and maternal hypertension (9) decrease the incidence of PDA. The effect of antenatal corticosteroids on closure of the ductus arteriosus is independent of their effect on lung maturation, and is most beneficial when corticosteroids are administered at least 24 hours before delivery. (10) Exogenous surfactant does not directly affect the ductus arteriosus, but can unmask a patent ductus by decreasing the pulmonary vascular resistance and thus allowing for increased left to right shunting. (1)

DIAGNOSIS

A consensus definition for hemodynamically significant PDA is lacking. The diagnosis is often suspected clinically, when an infant demonstrates signs of excessive shunting from the arterial to pulmonary circulation (Fig 1A and 1B):

- Continuous or systolic murmur; note, a "silent" PDA may also occur when the ductus shunt is large enough that nonturbulent flow fails to generate a detectible murmur.
- A low diastolic blood pressure (due to runoff into the ductus during diastole, more frequent in the most premature infants)
- A wide pulse pressure (due to ductus runoff or steal)
- Hypotension (especially in the most premature infants)
- Bounding pulses
- Increased serum creatinine concentration or oliguria
- Hepatomegaly

Signs of pulmonary edema are often seen, including tachypnea, decreased oxygen saturation, and increasing respiratory support. Chest radiography can show stigmata of pulmonary edema. The neonatal cardiac output can increase as much as 25% in an effort to overcome ductus steal. (11)

Clinical suspicion should be confirmed with echocardiography (Table 1). Ductus size alone is inadequate to attribute hemodynamic significance. Although an absolute transductus diameter of more than 1.5 to 1.7 mm by color Doppler (Fig 1C and 1D) has been associated with increased propensity for hypoperfusion, the exact diameter at which hemodynamic significance will occur varies by patient and postnatal age, depending on body size and many other factors, including oxygen saturation, surfactant administration, and furosemide. (12) El Hajjar et al suggest that by normalizing to body weight, a ductus diameter of more than or equal to 1.4 mm/kg is a more sensitive measure. (13) A large left-to-right shunt suggests a hemodynamically significant shunt. However, the degree of shunting depends in large part on pulmonary vascular resistance. A large ductus may not demonstrate large left-to-right flow if pulmonary vascular resistance is increased. In contrast, a right-to-left shunt may indicate significant pulmonary hypertension; acute closure of the ductus in this scenario is not indicated, because it could result in worsening right heart failure. With a large left-to-right shunt, indirect signs of obligate pulmonary hypertension may often be seen; this generally is not a contraindication to closure of the ductus but rather a natural consequence of excessive pulmonary blood flow.

Other echocardiographic criteria used to determine hemodynamic significance are the presence of reversal of

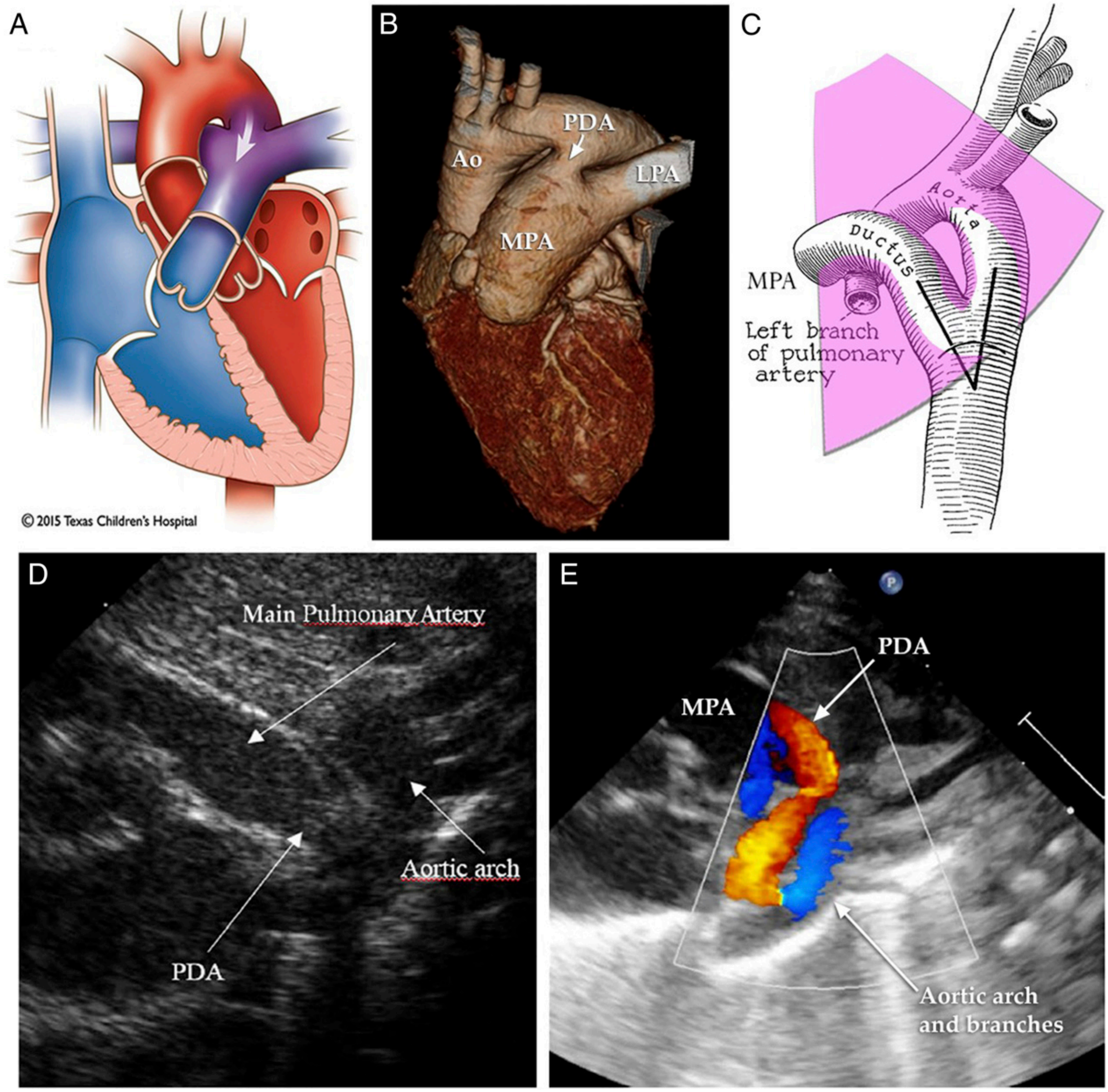

Figure. Evaluation of patent ductus arteriosus (PDA) with echocardiography. A, B. Left-to-right (L-R) shunt (indicated by arrows) via the ductus produces most of the physical signs and complications related to PDA. C–E. Short-axis and suprasternal views reveal structural relationships and color Doppler flow patterns indicative of L-R shunt across the ductus arteriosus. Ao=aorta; LPA=left pulmonary artery; MPA=main pulmonary artery. Images adapted or reprinted with permission from Texas Children's Hospital, (61)(62) and by Creative Commons license. (63)

forward flow in the descending aorta during diastole (indicating shunting through the PDA), and left atrial or ventricular dilation, which are the consequence of overcirculation of the pulmonary vascular bed and a chronic hyperdynamic state. Left-to-right flow across the intra-atrial septum is indicative of a large shunt. The ratio of the left ventricular output to superior vena cava flow is directly proportional to the ductus flow and, when greater than or equal to 4, may indicate hemodynamic significance. A left atrial to aortic root (LA/Ao) ratio is most sensitive when performed after day 1, and is considered abnormal if greater than 1.5. For comparison, the ductus is considered widely patent when the LA/Ao ratio is greater than 1.6, and closed when the ratio is 1.17. (14) If a cutoff of 1.4 is used, sensitivity of the LA/Ao ratio drops from 88% to between 50% and 79%. (14)(15)

PDA severity scores have been developed that combine various factors and can be used to predict higher likelihood of serious outcomes, such as death/chronic lung disease (CLD), periventricular leukomalacia, or necrotizing enterocolitis (NEC). The benefit of a scoring system is that it emphasizes the importance of examining multiple

TABLE 1. Echocardiographic Criteria Commonly Used to Diagnose PDA

INDICATOR	SENSITIVITY	SPECIFICITY
LA/Ao ratio ≥1.5 (20)	88%	95%
LVO/SVC ratio >4 (19)	92%	91%
Ductus diameter ≥1.5 mm (64) [≥1.4 mm] (19)(20)	95% (87%–92%)	80% (61%–91%)
Ductus diameter >1.4 mm/kg (19)	94%	90%
End diastolic flow velocity in left PA ≥0.2 m/s	82%	83%
Increased left ventricular output >60 mL/kg per minute above baseline (65)	N/A	N/A
Transductal velocity ratio <1.8 (66)	N/A	N/A

LA/Ao=left atrium to aortic ratio; LVO/SVC=left ventricular output to superior vena cava flow ratio; PA=pulmonary artery; N/A=not available.

TABLE 2. PDA Severity Scoring Systems (16)

SHAARE ZEDEK	EL-KHUFFASH
Ductus arteriosus diameter	Ductus arteriosus diameter
LA/Ao ratio	Gestation
Retrograde diastolic flow in the abdominal aorta	LVO[a]
Ductus arteriosus shunt flow pattern	V_{max} across PDA (m/s)
	Left ventricular late diastolic (a′) velocity

LA/Ao=left atrium to aortic ratio; LVO=left ventricular output; PDA=patent ductus arteriosus; Vmax=maximum flow velocity; VTI=velocity time interval.

[a] *(Aortic cross-sectional area × VTI × heart rate) ÷ weight*

factors when determining when and whether to intervene for a PDA. Table 2 shows a comparison of 2 separate scoring systems. Although they use different factors, they are equivalent in defining a hemodynamically significant PDA and prediction of CLD or death. The El-Khuffash score correlates significantly with NEC and the Shaare Zedek score correlates significantly with periventricular leukomalacia. (16)

Biomarkers

The N (amino)-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and mature B-type natriuretic peptide (BNP) may be useful in detecting a hemodynamically significant PDA. BNP is secreted and released by the ventricular myocardium when under stress from either increased volume or pressure. NT-proBNP, BNP, and cardiac troponin rise with increase in echocardiographic markers of PDA, and decrease following closure of the ductus. Not enough studies have been conducted to recommend these biomarkers for routine use in clinical management of a PDA. (17) They are likely to be of most benefit when the diagnosis of PDA is confirmed with echocardiography, but serial echocardiography to determine hemodynamic significance is unavailable, (12) or to shorten a course of pharmacologic treatment for a ductus. Shin et al stopped treatment with ibuprofen in infants with a PDA when BNP concentration dropped to less than 600 pg/mL, resulting in fewer doses of ibuprofen in the group whose treatment was tailored based on BNP. (18)

Biosensors

Bioengineering and analytical techniques have also been developed to monitor or detect PDA in preterm infants. Various approaches include interpretation of pulse oximetry information (perfusion index, plethysmography), (19)(20)(21) interpretation of transthoracic electrical signals (impedance, cardiometry, velocimetry, bioreactance), (22)(23)(24)(25) regional oxygenation (near-infrared spectroscopy), (26) alterations in skin microcirculation (side stream dark-field imaging, reflectance spectrophotometry), (27)(28) resonance Raman spectroscopy (Lauren J. Ruoss, personal communication, May 2018), and others.

OUTCOME

In healthy full-term infants, the ductus arteriosus closes within 48 to 72 hours. In premature infants born weighing more than 1,000 g, the ductus closes spontaneously in 67% by day 7 and in 94% by discharge. (5) Overall, only 3% of infants weighing more than 1,000 g may require intervention for a PDA. (1)(5)

However, in extremely premature infants weighing less than 1,000 g at birth (extremely low birthweight), 57% to 69% will still have a PDA at 7 to 10 days of age. (5)(9) Of those that close, up to 30% will reopen and may then reclose, or go on to become hemodynamically significant and require pharmacologic or surgical closure. When left untreated, the median time to ductus closure in this population is 56 days. (5) Some infants undergo spontaneous ductus closure as late as 24 months of age. (29)(30) Although these infants only account for a small proportion of premature infants and have small PDAs at the time of discharge, (31) the recognition that PDA closure occurs late in some cases has prompted some investigators to completely withhold retreatment. (32)(33) Because hemodynamically significant PDA has been associated with intraventricular hemorrhage (IVH), pulmonary hemorrhage, NEC, CLD, (9) and death, more substantial studies are required before nonintervention approaches can be widely adopted.

TREATMENT

Some clinicians choose a prophylactic approach to indomethacin treatment, with a goal of preventing IVH, PDA, and the adverse consequences that have been associated with PDA in extremely low-birthweight infants. (34) Despite successful reduction in short-term outcomes (IVH, pulmonary hemorrhage, hypotension, symptomatic PDA, need for ligation), long-term benefits are uncertain and infants may needlessly be exposed to a potentially harmful agent. (3)(35)(36)(37)(38)(39) On the other hand, NICUs with consistent, high-level use of a prophylactic strategy (40) or an echocardiography guided selective approach to prophylactic treatment (41) may have improved outcomes or less drug exposure. Well-designed studies are needed to clarify the risks/benefits of this approach.

The indications for treatment of a symptomatic PDA include respiratory compromise (eg, requiring persistent mechanical support), heart failure, or large left-to-right ductus shunt with evidence of hemodynamic compromise, such as reversal of flow in the descending aorta during diastole, oliguria or rising serum creatinine concentration, hypotension, or wide pulse pressure.

In patients of more than 1,000 g birthweight with few risk factors, a PDA can generally be successfully managed conservatively, with modest fluid restriction and use of positive end expiratory pressure to treat pulmonary edema. Certain diuretics, such as furosemide, can prevent a ductus from closing (42) and are not recommended in the first 1 to 3 weeks, when the greatest decrease in ductus diameter occurs spontaneously. Conservative measures also include avoidance of other drugs that promote ductus arteriosus relaxation (43) and proactive use of agents like caffeine that are associated with lower rates of PDA. (44)

In patients at higher risk of PDA, or who weigh less than 1,000 g at birth, conservative treatment is recommended before starting pharmacologic treatment. Treatment is generally not necessary in the first few days after birth when the pulmonary vascular resistance is still elevated. However, during the second week, treatment should be considered if conservative measures have failed to control pulmonary edema, or if there is cardiac or renal failure. After week 3, pharmacologic measures are less likely to be successful.

Early use of indomethacin to close a PDA soon after birth (day 1–2 of age), compared with waiting 3 to 4 days after diagnosis, decreases the risk for pulmonary hemorrhage and IVH, and need for ligation. Although PDA is associated with CLD, there is limited evidence to suggest that early pharmacologic closure improves incidence of CLD. (40)(45) Pharmacologic closure is associated with decreased pulmonary edema and improved alveolarization (in premature baboons). This may be due at least in part to a direct effect on the lung. Use of ibuprofen or indomethacin is associated with increased amiloride-sensitive alveolar epithelial sodium channels, increased lung water clearance, and improved lung compliance. (45)

PHARMACOLOGY

Three pharmacologic treatments are available to induce constriction of a PDA: indomethacin, ibuprofen, and acetaminophen (paracetamol) (Table 3). Indomethacin and ibuprofen are classic nonsteroidal anti-inflammatory drugs (NSAIDs), which nonselectively inhibit the cyclooxygenase enzymes, preventing the conversion of arachidonic acid to prostaglandins, which play a central role in maintaining ductus patency. Since 1976, indomethacin has been used to treat PDA in premature infants. Around the same time, ibuprofen was shown in lamb models to effect ductal closure but it was not widely used in human infants until the mid-1990s. Acetaminophen reduces prostaglandin synthesis by a different mode of action than most NSAIDs. Recent randomized clinical trials confirm its efficacy for PDA closure, though Food and Drug Administration approval for this indication is pending.

Indomethacin is administered intravenously. Enteral and rectal preparations are not recommended in infants because of increased risk for gastrointestinal bleeding.

In patients who receive a second course of indomethacin, only half will experience ductus closure. The odds of nonresponse to the second course of indomethacin are increased by 90% if there was nonresponse to the first course. Advancing gestational age appears to predict nonresponse to indomethacin. (46)

When studied head-to-head, indomethacin and ibuprofen have a similar efficacy (70%) for an initial course of 3 doses. Regardless of the treatment, there is about a 25% rate of reopening, especially in the most premature infants. Because of this high rate of reopening, some advocate a fourth dose of indomethacin, given 24 hours after the third dose.

Acetaminophen is speculated to decrease prostaglandin synthesis by interrupting prostaglandin synthesis at the

TABLE 3. **Common Dosing Regimens for Treatment of PDA**

MEDICATION	DOSING	CONTRAINDICATIONS	DRUG MONITORING
Acetaminophen	IV or PO: 7.5, 10, or 15 mg/kg per dose every 6–8 hours for 3–7 days (length determined by echo)	• Liver failure	AST, ALT, GGT and acetaminophen level before 9th dose
Ibuprofen	IV: 20 mg/kg followed by 10 mg/kg 24 hours apart for total 3 doses PO: 10 mg/kg followed by 5 mg/kg 24 hours apart for total 3 doses	• Significant renal impairment[a] • Necrotizing enterocolitis • Spontaneous intestinal perforation • Thrombocytopenia[b]	Urine output
Indomethacin	IV: 2–7 days of age: 0.2 mg/kg every 12 h for 3 doses, can be followed by a 4th dose 24 hours after the 3rd >7 days of age: 0.25 mg every 12 h for 3 doses, can be followed by a 4th dose 24 hours after the 3rd Enteral and rectal routes not recommended	• Significant renal impairment[a] • Necrotizing enterocolitis • Spontaneous intestinal perforation • Thrombocytopenia[b]	Urine output

ALT= alanine transaminase; AST= aspartate transaminase; echo=echocardiography; GGT=γ-glutamyl transferase; IV=intravenous; PDA=patent ductus arteriosus; PO=oral.

[a] *A hemodynamically significant PDA may cause renal impairment with oliguria and mild to modest increase in serum creatinine over baseline which is not a contraindication to pharmacologic treatment. Anuria or a significant increase in serum creatinine is a contraindication.*

[b] *Platelets $<50{,}000/\mu L$ ($<50\times10^9/L$).*

peroxidase site of prostaglandin H2 synthetase (cyclooxygenase). Acetaminophen for treatment of PDA is associated with less elevation in serum creatinine concentration and oliguria compared to ibuprofen or indomethacin, and less elevation in bilirubin compared to ibuprofen. (47) Acetaminophen has been used for rescue therapy after failed response to indomethacin in extremely premature infants, resulting in 46% of infants having a smaller or closed ductus. (48) When used as primary treatment, the efficacy ranges from 70% to 81%. (49)(50) Efficacy appears to be affected by both gestational age and postnatal age, with improved efficacy noted when treatment was started within the first week. (51) In fact, many case reports describing the use of acetaminophen start treatment as early as 2 to 3 days of age, early enough that many patients may go on to experience complete closure. Ductus closure rates are lower for the 3-day course (56%). (49)

There is a range of reported treatment regimens for acetaminophen, from 7.5 mg to 10 or 15 mg/kg every 6 hours for 3 to 7 days. Acetaminophen can be given orally, at the same dosage and interval, with similar reported efficacy as the intravenous route. (49) Kessel et al (52) showed that paracetamol levels in infants of age 26 to 30 weeks treated with 15 mg/kg per day orally remained mostly within the recommended range of 10 to 20 mg/mL for analgesia before the fifth and ninth doses, with only 2 of 8 patients exceeding the desired range before the ninth dose.

Treatment with acetaminophen can be associated with increase in serum concentration of liver enzymes in children and adults. This has been reported in preterm infants after as few as 4 doses of 15 mg/kg per day. Spontaneous resolution has been reported in all cases after the cessation of acetaminophen administration. Immaturity of the hepatic CYP enzymes responsible for acetaminophen metabolism may be protective against short-term toxicity in preterm infants; however, caution is warranted because liver injury is still possible. (53)

Whether or not to withhold enteral nutrition when a patient has a significant PDA or during pharmacologic treatment has long been a source of practice variability. A hemodynamically significant PDA can reduce forward blood flow to the superior mesenteric artery during diastole, and indomethacin acutely decreases gut blood flow. On the other hand, fasting is associated with intestinal mucosal atrophy which could increase the risk for NEC. A trial of premature infants being treated with indomethacin or ibuprofen and randomized to either receive 15 mL/kg of feeds per day or fast during treatment showed no difference in rates of NEC, and the patients randomized to continue feedings reached full feeds earlier than infants whose feeds were held. (54)

LIGATION

Surgical ligation is performed when a neonate has a hemodynamically significant PDA that results in cardiac dysfunction, renal failure, or respiratory failure. Ligation is typically performed with an open thoracic approach, and either using a metal clip or tying off the vessel. Intravascular approaches with placement of an occluding coil are available for patients weighing more than 5 kg. Trials are under way with products in development to accomplish catheter-based PDA closure in smaller patients. (55)

PDA ligation is associated with many adverse effects: vocal cord paralysis, postoperative hypotension, diaphragm paralysis, (56) bronchopulmonary dysplasia, and worse neurodevelopment. (57) Early PDA ligation is an independent risk factor for BPD (45) and worse neurodevelopment compared with ligation at a later age. (58) There does not appear to be increased risk of major complications when infants who have failed indomethacin treatment but do not have cardiopulmonary compromise are treated conservatively, rather than treated with ligation. (59) However, poor outcomes after PDA ligation may be overestimated by trial design, (60) suggesting that surgical approaches deserve full consideration for infants with refractory, symptomatic PDA.

CONCLUSION

PDA remains an important condition among premature infants born at less than 28 weeks' gestation. Recent advances include the addition of acetaminophen (paracetamol) to the arsenal of available treatments, and further support for conservative management of the asymptomatic or mildly symptomatic PDA, before the consideration of pharmacologic treatment. Improvements are still needed regarding standardized echocardiographic criteria, optimal timing of treatment (when indicated), dosing regimens for acetaminophen, and development of endovascular occlusive devices for the smallest preterm infants.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features of a preterm neonate with a patent ductus arteriosus.
- Recognize the laboratory, imaging, and other diagnostic features of a preterm neonate with a patent ductus arteriosus.
- Formulate a differential diagnosis of a preterm neonate with a patent ductus arteriosus.
- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for a preterm neonate with a patent ductus arteriosus.

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Diagnosis and Management of Patent Ductus Arteriosus

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Myocardial Disorders in the Neonate

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Education Gaps

1. Several physiologic changes take place in the myocardium after birth.
2. Knowledge about common primary myocardial disorders that present in the neonatal period has been limited.

Abstract

Myocardial disorders in the neonate could be a significant cause of morbidity and mortality. The neonatal myocardium is immature and undergoes several changes after birth. These include changes in the size of the myocardium, cellular transport of calcium, and utilization for fatty acid and glucose metabolism. Neonatal myocardium relies heavily on the heart rate to improve cardiac output. Myocardial disorders in the neonate can be classified as primary and secondary. Primary myocardial disorders have an inherent abnormality in the cardiac muscle and can be further subclassified based on the morphology and presentation. These include hypertrophic cardiomyopathy, dilated cardiomyopathy, and restrictive cardiomyopathy. Secondary myocardial disorders are usually caused by a systemic disorder that affects the cardiac muscle and function. These include inborn errors of metabolism, neuromuscular disorders, and mitochondrial disorders. The diagnosis and management of cardiomyopathy is very specific to the type of cardiomyopathy or underlying disorders. A team approach, including neonatology, genetics and metabolism, and cardiology and cardiac transplantation, is essential in managing these cases.

Objectives

After completing this article, readers should be able to:

1. Describe myocardial physiology and adaptation in the neonatal period.
2. List the common primary myocardial disorders.
3. Recognize myocardial disorders secondary to other diseases.

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ABBREVIATIONS

ARVC	arrhythmogenic right ventricular cardiomyopathy
DCM	dilated cardiomyopathy
ECG	electrocardiography
HCM	hypertrophic cardiomyopathy
IEM	inborn error of metabolism
LVOT	left ventricular outflow tract
MRI	magnetic resonance imaging

INTRODUCTION

The neonatal myocardium differs from the adult myocardium structurally as well as functionally. An understanding of the newborn myocardium and its disorders is crucial in the management of newborns. This review provides a summary of the structural and functional differences in the newborn myocardium and describes common myocardial disorders encountered in the neonatal period.

POSTNATAL CHANGES

The newborn myocardium is disorganized in structure and has a lower amount of contractile proteins than the adult mature myocardium. The neonatal myocardium also has decreased cellular transport. Both effects lead to a relatively impaired myocardial function in the neonate. (1) However, the role of the myocardium is similar in the neonate as in the adult: to increase heart rate and/or inotropy to improve cardiac output.

At birth, neonatal myocardial tissue responds to changes in the circulation quite rapidly. Both left ventricular mass and volume increase due to changes in the left and right ventricular workloads. (2) As the pulmonary vascular resistance drops, the right ventricular workload decreases and the left ventricle becomes the dominant ventricle after birth. (3) The number of myocytes increases initially in the first few of weeks after birth, and is then followed by the increase in cardiac mass, mostly as a result of hypertrophy of the myocytes. (4)

After birth, the neonatal myocyte changes from a relatively short and round shape into a longer and more slender shape as it matures. (1) The amount of mitochondria in the neonatal myocyte is localized centrally. With maturity, the amount of mitochondria increases and thus, the mature myocardium is able to use long-chain fatty acids rather than carbohydrates as its energy source. (5) In contrast, immature myocardium is more dependent on extracellular calcium for myocardial contraction. Because the neonate has a lower amount of calcium channels compared with later in life, the neonatal myocardium has less functional reserve. (6) The fetal and neonatal myocardium also has a limited ability to respond to an increased afterload, and ventricular compliance is relatively decreased compared with the adult. Thus, a newborn heart is stiffer and requires relatively small volumes to achieve a desired filling pressure.

Myocardial disorders account for only approximately 1% of childhood cardiac disease (7) and can be classified into 2 major groups based on the organ involvement. (8) Primary cardiomyopathy solely affects the heart muscle and is relatively infrequent. Secondary cardiomyopathies have myocardial involvement as a part of a generalized systemic disorder.

PRIMARY CARDIOMYOPATHY

The clinical disease process of primary cardiomyopathies predominantly involves the myocardium. Primary cardiomyopathy can be further divided into 3 groups: genetic, mixed, and acquired (Table). Not all of these disorders manifest in the neonatal period but most of them are diagnosed in the neonatal period because of a family history of a similar disorder. The types seen in the neonatal period are usually the most severe.

TABLE. **Causes of Primary Cardiomyopathy**

1. Genetic
a. Hypertrophic cardiomyopathy
b. Arrhythmogenic right ventricular cardiomyopathy
c. Left ventricular noncompaction cardiomyopathy
d. Glycogen storage disorders
i. *PRKAG2*
ii. Danon cardiomyopathy
e. Conduction defects
f. Mitochondrial myopathies
g. Ion channel disorders
i. Long QT syndrome
ii. Brugada syndrome
iii. Short QT syndrome
iv. Catecholaminergic polymorphic ventricular tachycardia
v. Asian sudden unexplained nocturnal death syndrome
2. Mixed
a. Dilated cardiomyopathy
b. Restrictive cardiomyopathy
3. Acquired
a. Inflammatory (myocarditis)
b. Stress-provoked (“tako-tsubo”)
c. Peripartum
d. Tachycardia-induced
e. Infant of insulin-dependent diabetic mother
f. Ischemia/hypoxia

Genetic

Hypertrophic Cardiomyopathy. Idiopathic hypertrophic cardiomyopathy (HCM) is caused by mutations of the cardiac contractile proteins, most commonly β-myosin heavy chain and myosin-binding protein C. (8) In patients with HCM, the cardiac mass and wall thickness are increased and generally affect the left ventricle. A murmur is usually the presenting feature. (9) Affected infants can have various clinical findings, including marked congestive heart failure and cardiomegaly on chest radiography. Electrocardiography (ECG) shows left ventricular hypertrophy with ST-T changes (Fig 1). Echocardiography (Fig 2) usually confirms the diagnosis in the absence of other reasons for ventricular hypertrophy such as maternal diabetes, steroid exposure, or neonatal hypertension. Cardiac magnetic resonance imaging (MRI) can demonstrate myocardial fibrosis and scarring.

The goal of management for patients with HCM is symptomatic relief and prolonging survival. β-Blockers are the most commonly used agents for the purpose of decreasing gradients in acute settings. (10)(11) These agents help to reduce left ventricular outflow gradients by decreasing contractility, wall tension, and myocardial oxygen demand. At the author's institution, propranolol 2 mg/kg per day is used in 3 divided doses. The dose can be titrated based on symptoms, heart rate, blood pressure, and response. In neonates with left ventricular outflow tract (LVOT) obstruction, caution is required when using vasodilators or positive ionotropic agents because of the risk of increasing the LVOT gradient. Diuretics are generally counterproductive as they decrease the patient's overall volume, and thus decrease the ventricular cavity.

In general, the prognosis of neonatal HCM is poor, especially if the neonate has congestive heart failure. (9) Patients with inborn errors of metabolism (IEM) and malformation syndrome usually have a poorer prognosis than those with idiopathic infantile HCM, with mean 5-year survival rates of 41%, 74%, and 82%, respectively. (12) HCM secondary to disorders such as hypertension, steroid use, and maternal diabetes have a very good prognosis, with a reversal of the cardiomyopathy with conservative management or treatment of the underlying disorder.

Arrhythmogenic Right Ventricular Cardiomyopathy. This type usually involves the right ventricle with loss of myocytes and fatty or fibroblast tissue replacement. Arrhythmogenic right ventricular cardiomyopathy (ARVC) has a broad clinical spectrum, but most patients present with ventricular tachyarrhythmias. It rarely presents during infancy. ARVC typically has an autosomal dominant pattern of inheritance and the diagnosis is usually based on family history, characteristic findings on ECG, and cardiac MRI.

Left Ventricle Noncompaction Cardiomyopathy. This type is characterized by a spongy appearance of the left ventricular myocardium on echocardiography (Fig 3). Noncompaction usually involves the apical portion of the left ventricle with deep intratrabecular recesses (Fig 3) communicating with the ventricular cavity; this results from an

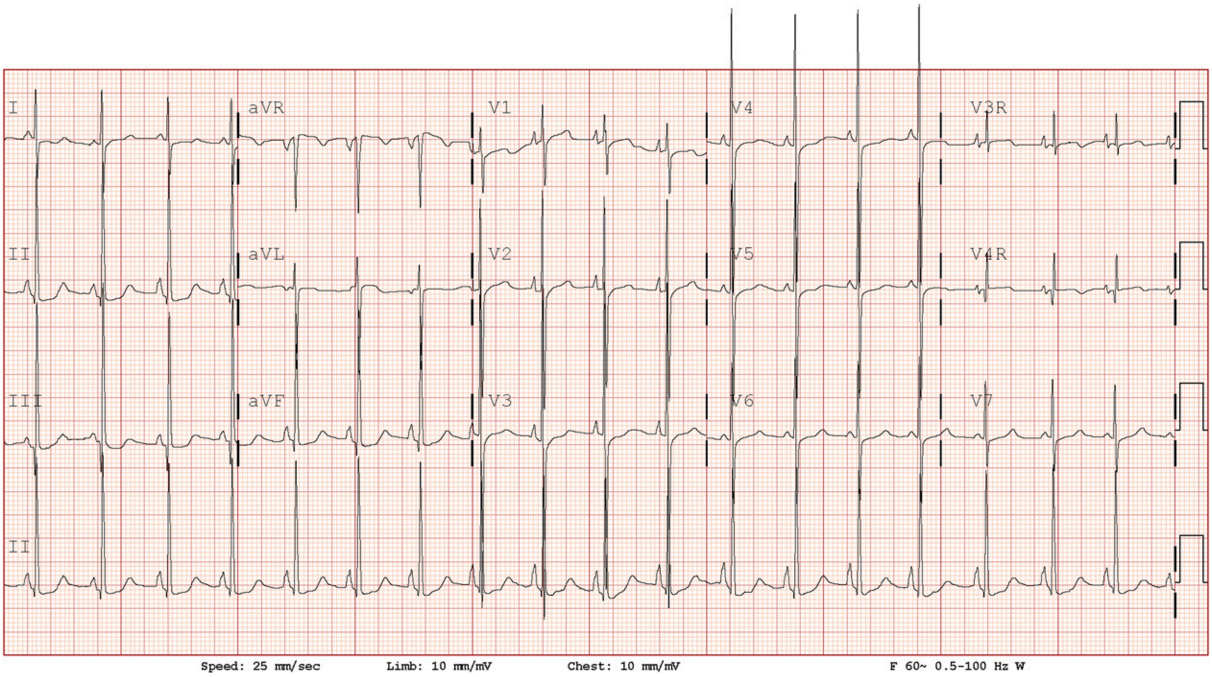

Figure 1. Electrocardiogram showing left ventricular hypertrophy in a patient with hypertrophic cardiomyopathy.

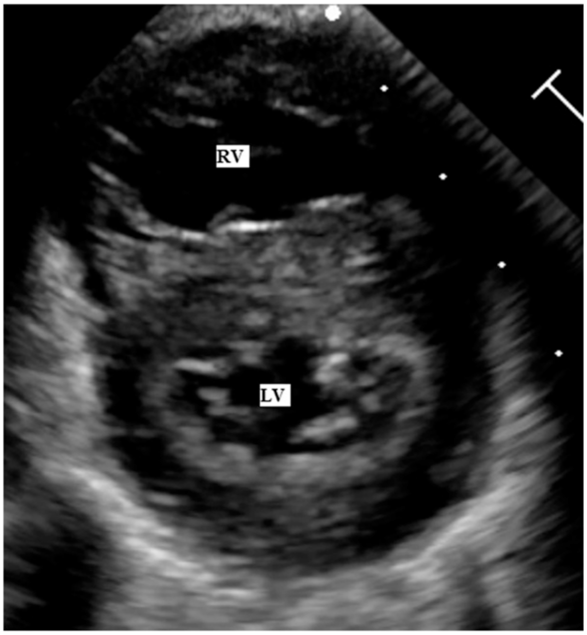

Figure 2. Echocardiogram of a neonate showing left ventricular hypertrophy with more pronounced septal hypertrophy. LV=left ventricle; RV=right ventricle.

arrest in normal cardiac embryogenesis. (13) Left ventricle noncompaction cardiomyopathy may be an isolated abnormality or associated with other congenital heart diseases such as LVOT abnormalities, Ebstein anomaly, and tetralogy of Fallot. (14) The diagnosis is usually made with 2-dimensional echocardiography or cardiac MRI. Presentation in the neonatal period is usually associated with poor prognosis, leading to death or a need for transplantation early in life.

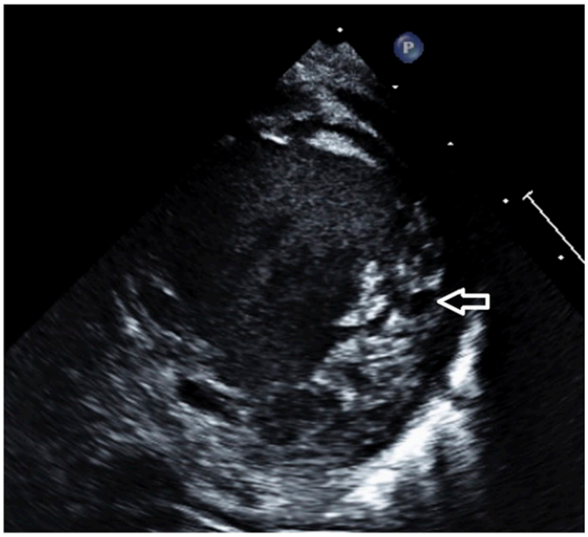

Figure 3. Echocardiogram of a neonate with left ventricle noncompaction cardiomyopathy. Arrow shows the deep trabecular recess.

Conduction System Diseases. As depicted in the Table, there are various conduction system abnormalities and ion channel disorders that are classified as cardiomyopathies. Although classified in this way, the myocardium is usually normal in these disorders. These disorders are characterized by ECG changes and arrhythmias. Cardiac function could be affected secondary to an arrhythmia. Several specific genes have been connected to these disorders.

Mixed

Dilated Cardiomyopathy. Dilated cardiomyopathy (DCM) is more common than HCM or restrictive cardiomyopathy. (15) The prevalence is about 1 in 2,500 in the general population and it is the most frequent cause of heart transplantation. DCM can result from a primary abnormality in the cardiac myocyte or can be secondary to a wide range of other disorders such as myocarditis. Other secondary causes include autoimmune and systemic disorders, pheochromocytoma, neuromuscular disorders, and mitochondrial, endocrine, and nutritional disorders. About 20% to 35% of DCM cases are familial. (8) Inheritance is heterogeneous, with most cases being autosomal dominant.

Patients with DCM usually present at a later age and rarely in the neonatal period. This disorder is characterized by ventricular enlargement and decreased systolic function; affected patients present with symptoms of low cardiac output such as pallor, irritability, and diaphoresis. (7) Physical findings include tachypnea, tachycardia, narrow pulse pressure, and hepatomegaly. ECG shows flattening of the T wave with possible depression of the ST segments. Cardiomegaly is evident on chest radiography. Echocardiography is diagnostic. Cardiac MRI is often helpful in identifying myocardial fibrosis and scarring but may be difficult to interpret in neonates with increased heart rates. Management includes treatment of heart failure. In contrast to HCM, vasodilators, diuretics, and inotropes are useful in the management of DCM. If management is unsuccessful, patients can develop severe heart failure, arrhythmias, or sudden death.

Restrictive Cardiomyopathy. This is an extremely rare condition in which the ventricular cavities are small and diastolic function is impaired, involving both but predominantly the left ventricle. (7) The systolic function is normal, at least initially. It is very rare in neonates. Affected neonates present with signs and symptoms of congestive heart failure. ECG often shows conduction abnormalities and evidence of ischemia at higher heart rates. Echocardiography shows normal or small ventricles with dilation of both atria. Restrictive cardiomyopathy should be differentiated from constrictive pericarditis as affected patients could have similar presentations. The prognosis is poor. Survival without transplantation was reported at 39% in 1 center with children of all ages. (16)

Acquired Cardiomyopathy

Myocarditis. Myocarditis is the most common form of acquired cardiomyopathy in neonates. It is caused by acute or chronic inflammation of the myocardium as a result of a wide variety of toxins or infections. The most common infectious agent is viral (eg, Coxsackie virus, adenovirus, parvovirus, human immunodeficiency virus). Other infectious causes include bacterial, fungal, and parasitic. Most of these infections are encountered outside the neonatal period. Endocardial fibroelastosis is a type of cardiomyopathy that can be caused by an intrauterine infection with the mumps virus. (17) The clinical presentation of myocarditis is similar to that of dilated cardiomyopathy.

Maternal Diabetes. Infants of diabetic mothers may have a transient hypertrophic cardiomyopathy with spontaneous regression during the first 6 months of age when insulin levels normalize. (18) It is a complication in 25% to 30% of infants born to women with gestational or prepregnancy diabetes. The ventricular septum is preferentially affected but both the right and left ventricle free walls may also be involved. (19)

Ischemia/Hypoxia. Neonatal myocardial infarction is rare, with a few case reports in the literature. (20)(21) Neonates can have a good recovery with interventions such as extracorporeal membrane oxygenation or catheter interventions. (22)(23)

Birth asphyxia is associated with several cardiovascular changes. Ongoing severe asphyxia is associated with significantly reduced ventricular output and stroke volume. (24) The cause of eventual myocardial dysfunction is multifactorial, including low heart rate associated with asphyxia, acidosis, and ischemic myocardial injury. (25)(26) Affected newborns have an increased troponin level, which has been associated with myocardial damage. (27) Clinical management of cardiac dysfunction relies on maintaining adequate perfusion to organs by maintaining blood pressure and cardiac contractility.

SECONDARY CARDIOMYOPATHY

The myocardial involvement in these disorders is secondary to various multisystem disorders. The frequency and severity of the myocardial involvement varies significantly among these diseases. Some of these disorders are very uncommon, and even then the involvement might not be seen in the neonatal period. IEMs are among the most common causes of secondary cardiomyopathy.

Inborn Errors of Metabolism

Approximately 5% to 26% of infants and children with cardiomyopathy have an IEM. (28) In some cases, the cardiomyopathy dominates the clinical presentation and is the major cause of death. More than 40 disorders are known to cause IEM cardiomyopathy, including fatty acid oxidation defects, organic acidemias, amino acid disorders, glycogen storage diseases, and congenital disorders of glycosylation as well as peroxisomal, mitochondrial, and lysosomal storage disorders. (29) Most of these present in infancy or early childhood with multiorgan dysfunction. Many of these disorders are treatable by targeting the underlying pathophysiology of the disease. Some of the cardiomyopathies could also be reversed by treating the underlying disorder.

IEMs cause cardiomyopathy through various mechanisms. (29) The first is deposition or infiltration of a substrate within the myocyte. These deposits involve large macromolecules such as triglycerides, glycogen, and lysosomal substrates. This has a mechanical effect on the myocyte function. A second mechanism is impaired energy production within the myocyte. These include oxidative phosphorylation defects. A third mechanism is production of toxic metabolites such as organic acidemias.

Each IEM is associated with a specific type of cardiomyopathy, usually DCM or HCM. Of the HCMs caused by IEMs, 50% are due to glycogen storage diseases, of which Pompe disease is the most common. (15) Infants with Pompe disease present with hypotonia, muscle weakness, an enlarged tongue, and congestive heart failure. ECG shows tall QRS waves and short PR intervals. Chest radiography demonstrates cardiomegaly while echocardiography shows severe left ventricular hypertrophy with or without LVOT obstruction. In the pediatric cardiomyopathy registry, fatty acid oxidation defects and oxidative phosphorylation defects comprise 25% of IEM-related cardiomyopathies, with most leading to DCM.

Most cardiomyopathies caused by IEMs present during infancy or early childhood. Cardiomyopathy may be the dominant clinical presentation. An extensive evaluation often reveals signs of multisystem involvement, including physical findings (coarse facial features, cloudy corneas or cataracts, and hepatosplenomegaly), neurologic abnormalities, skeletal myopathy, and skeletal abnormalities. (29) Early diagnosis is key to management of these disorders. Management is aimed at correction of the underlying metabolic disorder.

Neuromuscular/Neurologic Disorders

Many neuromuscular disorders can have associated cardiomyopathies but it is unusual for cardiomyopathy to be the presenting symptom. (30) Duchenne and Becker muscular dystrophies are among the most common myopathies associated with cardiomyopathy. The heart is usually affected later in life and affected infants usually are asymptomatic.

Myotonic dystrophy is the most common form of muscular dystrophy. The clinical presentation depends on the form of the disease: congenital, infantile, juvenile, or adult-onset. The severity depends on the number of CTG repeats, with the most severe disease developing in patients with more than 1,000 repeats. (30) The congenital form presents with decreased movements in fetal life, hypotonia, and respiratory failure. Cardiac involvement appears in the second decade of life. Cardiovascular symptoms in these disorders are not overt because of the low level of physical activity.

Mitochondrial Disorders

Mitochondrial disorders are a heterogeneous group of multisystem diseases secondary to mutations in nuclear or mitochondrial DNA. These can be diagnosed at any age depending on the severity of the disease. Cardiac manifestations could include HCM or DCM. (31) Cardiac involvement is typical of certain abnormalities.

Kearns-Sayre syndrome is a mitochondrial myopathy consisting of ptosis, ophthalmoplegia, and retinal pigmentation; affected patients are predisposed to atrioventricular conduction abnormalities.

Patients with myoclonic epilepsy with ragged red fibers or mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes could develop HCM or DCM.

The most common infantile mitochondrial disorder is Leigh syndrome, a progressive neurodegenerative disorder. (31) This syndrome is characterized by gliosis, demyelination, capillary necrosis, and necrosis in the brain. Cardiac involvement could be in the form of HCM and conduction defects such as Wolff-Parkinson-White syndrome.

Sengers syndrome presents with congenital cataracts, HCM, mitochondrial myopathy, and lactic acidosis. Affected patients can present with a severe neonatal form that causes infantile death or a more benign form with longer survival. The cause of death is usually HCM.

Barth syndrome is an X-linked genetic disorder characterized by cardiomyopathy, intermittent neutropenia, muscular weakness, and 3-methyl-glutanic aciduria. It is caused by mutation in the tafazzin (*TAZ*) gene. Affected patients have a high mortality rate during infancy as a result of cardiac dysfunction.

DIAGNOSIS AND MANAGEMENT

The evaluation of patients with a cardiomyopathy is methodical, and involves evaluation by multiple specialties including neonatology, cardiology, metabolism, and genetics. Psychological and family support should be available, because quite often these patients have an underlying systemic or genetic disorder that requires extensive counseling and guidance. The cardiac transplant team should be involved when providers suspect a possible cardiomyopathy. If relevant, a muscle or myocardial biopsy can help to identify the underlying neuromuscular disorder. Management of secondary cardiomyopathies often involves correction of the underlying metabolic or genetic disorders. The role of immunoglobulin administration in neonatal myocarditis is uncertain. Cardiac failure is often managed symptomatically with the use of diuretics, afterload-reducing agents in infants with DCM, and β-blockers in patients with HCM.

CONCLUSION

Myocardial disorders in the neonatal period are not uncommon and may have a heterogeneous presentation. Patients with a primary cardiomyopathy usually do not present during the neonatal period. If symptoms are present, the condition is usually associated with a poor prognosis. Patients with a secondary cardiomyopathy may present in the neonatal period, depending on the severity of the underlying defect.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the anatomy and pathophysiology (including genetics) of an infant with a condition affecting myocardial performance.
- Recognize the clinical features in an infant with a condition affecting myocardial performance.
- Recognize the laboratory, imaging, and other diagnostic features of an infant with a condition affecting myocardial performance.
- Formulate a differential diagnosis of an infant with a condition affecting myocardial performance.
- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for an infant with a condition affecting myocardial performance.

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1 Late-Onset Hypoglycemia in an Extremely Low-Birthweight Infant

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PRESENTATION

An 800-g extremely low-birthweight female (25 5/7 weeks) twin A of a dichorionic-diamniotic gestation is born via primary low transverse cesarean delivery to a 37-year-old gravida 5, para 0-4-0-0 woman. The mother of the child is group B *Streptococcus* positive, and received 1 dose of penicillin less than 4 hours before delivery. Results of other antenatal testing had been reassuring. Preterm delivery is indicated for prolonged rupture of membranes of twin B, and the mother had received 2 doses of betamethasone 24 hours apart at the estimated 24th week of gestation.

The neonate has Apgar scores of 3 and 8 at 1 and 5 minutes, respectively. She is stabilized on continuous positive airway pressure and transferred to the NICU by 5 minutes after birth. In the NICU, she requires intubation and fraction of inspired oxygen greater than 60% to maintain oxygenation. An umbilical artery catheter and umbilical venous catheter are established and she is treated with ampicillin and gentamicin. She initially has hypotension requiring a 10-mL/kg bolus of normal saline without improvement, necessitating institution of a dopamine drip titrated from 2 to 5 μg/kg per minute to maintain mean arterial pressures above 25 mm Hg. She is started on intravenous fluids of 100 mL/kg per day with a glucose infusion rate (GIR) of 5 mg/kg per minute, which is reduced to 3.1 mg/kg per minute by 1 day after birth because of worsening hyperglycemia. Despite serial reduction of GIR, she persistently demonstrates capillary blood glucose levels above 230 mg/dL (12.7 mmol/L). Thus, a 0.1 U/kg (0.08 U) dose of insulin is given intravenously. Shortly after the insulin administration, the NICU team is notified by the inpatient pharmacy that because of a dilutional error, the dose of insulin administered was 8 U, or 100 times the ordered dose.

DIFFERENTIAL DIAGNOSIS

Neurologic signs in the neonate such as jitteriness, lethargy, weak suck, and seizures should always prompt consideration of hypoglycemia as a cause. Though these signs are nonspecific, untreated hypoglycemia can have devastating consequences. In addition, diagnosis and treatment are relatively quick with few lasting side effects.

The differential diagnosis of hypoglycemia in the neonatal period is broad. In premature neonates who have not experienced the period of rapid glycogen accrual in late gestation, limited hepatic glycogen stores can lead to transient hypoglycemia. This can be further exacerbated by aberrant patterns of insulin secretion and distorted responses to blood glucose concentrations. Small-for-gestational age infants are also at increased risk for hypoglycemia because of inadequate substrate for glycogen synthesis. Further, infants of multiple gestations may also be at risk for hypoglycemia because of relative placental insufficiency. The most common population to experience neonatal hypoglycemia is infants born to diabetic mothers. These neonates have increased secretion of insulin because of increased glucose concentrations in utero. After delivery, the neonate is no longer exposed to maternal hyperglycemia via placental transport, but increased insulin secretion can persist. This increased insulin secretion can cause decreased hepatic glucose production despite decreasing blood glucose levels due to the inhibitory effect of insulin on glycogenolysis and lipolysis. Increased peripheral utilization of glucose due to sepsis and inflammatory consumption is a common culprit causing glucose irregularity. Hypoglycemia that lasts for more than 5 to 7 days is uncommon and is more likely to be the result of congenital hyperinsulinism or inborn errors of metabolism. These disorders are rare and should be considered only after ruling out more common causes. In the setting of postnatal insulin administration, iatrogenic hyperinsulinism should also be considered.

THE CONDITION

Errors are common in the pediatric setting, and occur more commonly in the NICU than in other inpatient pediatric wards. Particularly in the NICU, many of these errors are medication related. Medication errors are defined as any mistakes that occur during the medication use process, including prescribing, dispensing, transcribing, administering, and monitoring. (1) In a sample of 1,230 reports of medical errors in 40 different NICUs, Suresh et al found that 47% of medical errors were medication errors. Of these medication errors, 25% were due to medication dispensing. (2) Rapidly changing weights, high acuity, and need for dilution all contribute to these higher rates of medication errors in the NICU. (3) Medications such as insulin, which must be serially diluted from stock solutions, further compound this risk and increase the potential for 10-fold and 100-fold errors. (4) The neonatal population is particularly susceptible to harm from medication errors because of their decreased physiologic reserve and inability to buffer harm. (5) However, in the largest available analysis of NICU errors, Stavroudis et al found that fewer than 5% of these medication errors lead to harm to the patient. (6)

MANAGEMENT AND CLINICAL PROGRESS

The infant was diagnosed with insulin overdose and the family was immediately notified. The goal of management for insulin overdose is rapid correction of hypoglycemia and avoidance of future episodes. Thus, the neonate was given strict goal-directed therapies. First, 30-minute capillary blood glucose checks were instituted. If the screened glucose value registered less than 100 mg/dL (5.5 mmol/L), the GIR would be increased by 2 mg/kg per minute. If the glucose level became less than 80 mg/dL (4.4 mmol/L), the GIR would be increased by 2 mg/kg per minute, and a bolus of 200 mg/kg of 10% dextrose and water (2 mL/kg of D10W) would be administered. If the glucose level became less than 50 mg/dL (2.7 mmol/L), the GIR would be increased by 2 mg/kg per min and 4 mL/kg of D10W would be administered. Finally, if the glucose level became undetectable by capillary specimen, glucagon 0.2 mg/kg would be administered. Over the course of the next 3 hours, GIR was increased in a staggered fashion from 3.1 mg/kg per minute to a maximum of 10.6 mg/kg per minute with a glucose nadir of 95 mg/dL (5.2 mmol/L). The infant never required glucagon or a bolus of D10W and hypoglycemia resolved within 12 hours of the event.

This goal-directed therapy plan is supported by the literature on acute management of hyperinsulinemic hypoglycemia; administration of "miniboluses" of D10W in conjunction with an increase in GIR has been shown to normalize blood glucose concentration more rapidly than glucose infusion alone. (7)(8)

Lessons for the Clinician

- Hypoglycemia in the neonatal setting can have nonspecific signs and symptoms.
- Medication errors are common in the pediatric setting, and more common in the NICU.
- Medications such as insulin which require serial dilution are prone to 10-fold and 100-fold errors.
- Iatrogenic insulin overdose can be managed by increased glucose infusion rate in conjunction with the minibolus method.

ACKNOWLEDGMENTS

The authors wish to thank Maj Nicholas Carr, DO, for providing the management strategy outlined in this case; Col Nicola Choate, MD, for subspecialty consultation in the care of this patient; and Jason Neill, PharmD, for his help providing process improvement strategies related to this case.

Note. The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the US Army Medical Department, the US

Army Office of the Surgeon General, the Department of the Air Force, the Department of the Army or the Department of Defense, or the US Government.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes (including hyperinsulinemic hypoglycemia) of neonatal hypoglycemia syndromes.

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Case 1: Late-Onset Hypoglycemia in an Extremely Low-Birthweight Infant

Adharsh Ponnapakkam, Patrick Reeves and Carrie Litke-Wager

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2 A Large Prenatally Undiagnosed Mass in a Preterm Infant, What Could It Be?

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AUTHOR DISCLOSURE Drs Ibrahim, Pavageau, Miller, Timmons, Wickiser, Piper, Dariya, and Brion have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2.2-kg female infant is born at 28 4/7 weeks' gestation to a 21-year-old gravida 1, para 0 woman with adequate prenatal care. During pregnancy, the mother is treated for *Chlamydia* with repeat negative cultures. She has negative serologies and a normal fetal ultrasonographic scan at 20 weeks' gestation. Delivery is via cesarean section due to premature labor and frank breech presentation. At delivery, the infant is noted to have no respiratory effort and a large sacrococcygeal mass (Fig 1). Positive pressure ventilation is started and the infant undergoes intubation 3 minutes after birth.

The admission physical examination findings are significant for a sacrococcygeal nodular, firm and nonpulsatile 20×30–cm mass, with minimal ulceration that is displacing the lower limbs anteriorly. Magnetic resonance imaging (MRI) of the pelvis shows a presacral mass with a large external component and relatively small internal component; the cephalad portion of the mass occurs at the level of L5, splaying the aortic bifurcation (Fig 2). The infant's vital signs are stable with minimal ventilatory support. Laboratory studies are positive for anemia (hemoglobin 11.4 g/dL [114 g/L]), a normal α-fetoprotein (AFP) level for gestational age (60,500 ng/mL [60,500 μg/L]), and a slightly elevated aspartate aminotransferase level (141 IU/L [2.35 μkat/L]).

On day 2 after birth, the infant develops hypotension and worsening respiratory failure; she is started on inotropes and high-frequency oscillation. The lesion becomes more tense and darker in color, concerning for intralesional hemorrhage. The infant also develops thrombocytopenia (platelets 66,000/μL [60×10^9/L]) and receives multiple platelet and red blood cell transfusions in preparation for surgery. Resection of the mass takes place at the bedside because of the infant's hemodynamic instability and inability to be safely transported with the oscillator to the operating room. The 8-hour procedure is conducted in 2 stages. The initial abdominal approach allows for ligation of the 2 small feeding vessels emerging from the internal iliacs. The infant is then placed in a prone position, for the subsequent sacral approach to resect the mass including the coccyx (Fig 3). The infant has an estimated blood loss of 400 mL, and receives large-volume

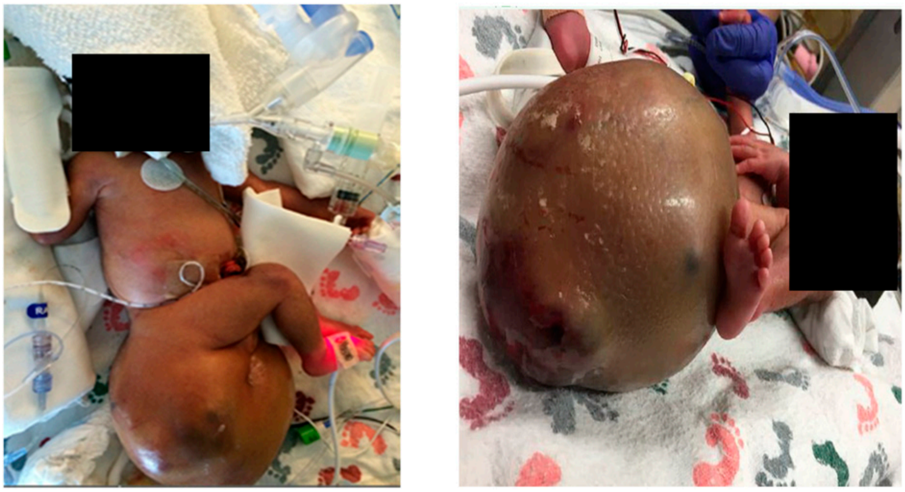
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Figure 1. Infant at delivery noted to have large sacrococcygeal teratoma.

fluid resuscitation (~240 mL/kg) and inotropic and vasopressor support. Inotropic support and high-frequency ventilation are discontinued within 24 hours. She is started on enteral feeds 1 week after surgery and is discharged from the hospital at 38 weeks' postmenstrual age. Macroscopically, the resection specimen is a 715-g predominantly solid mass with cystic areas, and measures 14×13.5×11.7 cm. Microscopic examination reveals a mixture of tissues representing all 3 embryonic layers, including brain and squamous epithelium (ectoderm); ciliated respiratory type epithelium; mucous glands with goblet cells and liver (endoderm); and kidney, smooth muscle, and cartilage (mesoderm), along with immature neuroectodermal epithelial elements, which defined the teratoma as immature (Fig 4). AFP levels were followed, reaching their highest value 1 month after birth (416,195 ng/mL [416,195 μg/L]) followed by a steady decline.

DISCUSSION

The Condition

Teratoma is a Greek word that translates into "monster tumor."(1)(2) Teratomas are the most common germ cell tumors of the fetus and neonate. The term *teratoma* was first applied by Virchow in 1869 to a tumor originating from the sacrococcygeal area. Sacrococcygeal teratoma (SCT), the most common congenital tumor, accounts for about 35% to 60% of all teratomas and occurs in 1 in 35,000 to 40,000 live births. It is more prevalent in female fetuses, occurring at a female-to-male ratio of 4:1.

Teratomas can be solid or cystic, benign or malignant. They are usually composed of germ cell tissues including the 3 embryonic layers (endoderm, mesoderm, and ectoderm). Teratomas can occur anywhere in the body particularly along the midline. In neonates, teratomas are most often located within the sacral area.

Three theories for the origin of teratomas have been proposed. (1) The first theory postulates that teratomas originate from the endodermal cells of the yolk sac near the origin of the allantois (totipotent primordial germ cells). During the 4th and 5th week of embryonic development, these cells migrate to the gonadal ridges but if they miss their migration target, they may give rise to a teratoma anywhere from the brain to the coccygeal area. Another theory proposes that teratomas develop from the remnants of the primitive node. During the 3rd week, midline cells at the caudal end of the embryo give rise to all 3 germ layers

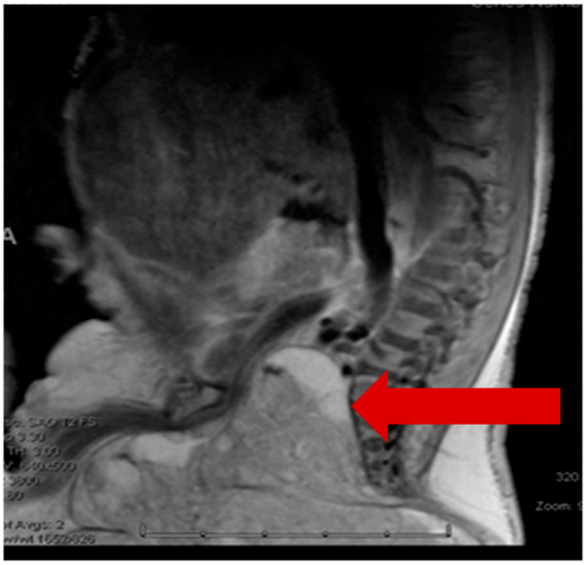

Figure 2. Magnetic resonance imaging scan of the pelvis showed a presacral mass (red arrow) with a large external component and relatively small internal component.

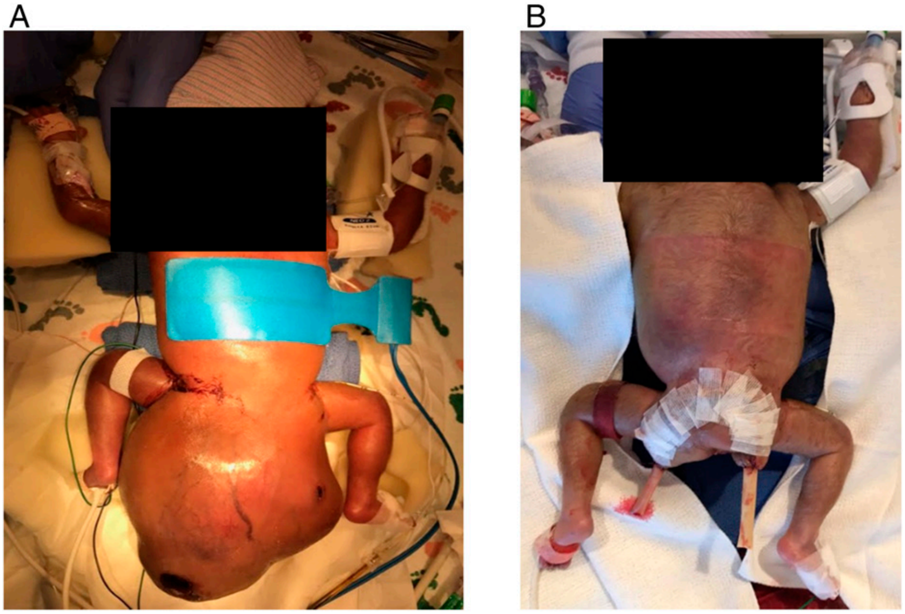

Figure 3. Photograph of the neonate with a sacrococcygeal teratoma mass before (A) and after (B) resection.

and the remaining primitive streak shortens and disappears. The last theory describes teratomas as incomplete twinning.

SCTs can be part of the Currarino triad (anorectal malformation, sacral anomaly, presacral mass). Rare syndromes associated with teratomas are Klinefelter syndrome (strongly associated with mediastinal teratoma), trisomy 13, trisomy 21, and Beckwith-Wiedemann syndrome as well as Proteus and Schinzel-Giedion syndromes. Teratomas in most of the cases are isolated in presentation.

Teratomas can be gonadal or extragonadal. In 1974, Altman et al classified SCTs into 4 types based on location (3):

Type I: The most common type is predominantly external with a minimal presacral component.

Type II: Tumors are external with a significant intrapelvic component.

Type III: Tumors are external but with significant pelvic and intraabdominal extension

Type IV: Entirely presacral tumors, with no external components.

Histologically, teratomas are classified as mature or immature based on the presence of the immature neuroectodermal components. However, grading of immature teratomas is of little importance in neonates, as the management and prognosis are not altered. A solid tumor has components of skin elements, neural tissue, fat, muscle, and cartilage as well as hair or bone. Rare parts such as respiratory epithelium, fingers, teeth, rudimentary heart, or a complete eye have been described.

Athough the majority of SCTs are benign, 11% to 35% will contain malignant elements. Malignancy risk increases with age, in males, and with incomplete resection. The most common malignant component is an AFP-producing yolk sac tumor. Histologic detection of small foci of yolk sac tumor may be difficult in very large tumors, and AFP levels may be difficult to interpret because of the wide range of normal values in infants. A mature teratoma may reoccur months or even years after resection as a malignant yolk sac tumor (10%).

In utero, SCTs can cause maternal proteinuria, hypertension, or edema, symptoms similar to preeclampsia. "Maternal mirror syndrome" or "Ballantyne syndrome" has been reported in some cases. Prenatal SCTs may go unnoticed until late in gestation. However, an elevation in maternal serum AFP from an incompletely skin-covered mass could be an indication.

Polyhydramnios associated with fetal hydrops or placental edema can develop because of fetal anemia secondary to SCT tumor hemorrhage. Less commonly, oligohydramnios from obstruction of the fetal urinary tract has been reported. SCTs, particularly solid tumors, can be highly vascular, and a fetus can develop high cardiac output failure, anemia, and ultimately hydrops.

The 2-dimensional ultrasonography performed during pregnancy has resulted in a high rate of SCT detection. The detection of solid components within a tumor is critical because it is associated with a high risk of malignancy and fetal hydrops due to high cardiac output. Once a sacral mass is identified, an evaluation of the distal spine and brain is warranted to rule out meningomyelocele. MRI is superior to ultrasonography, with regard to contrast resolution, improved tumor demarcation, and vascular perfusion of a mass, as well

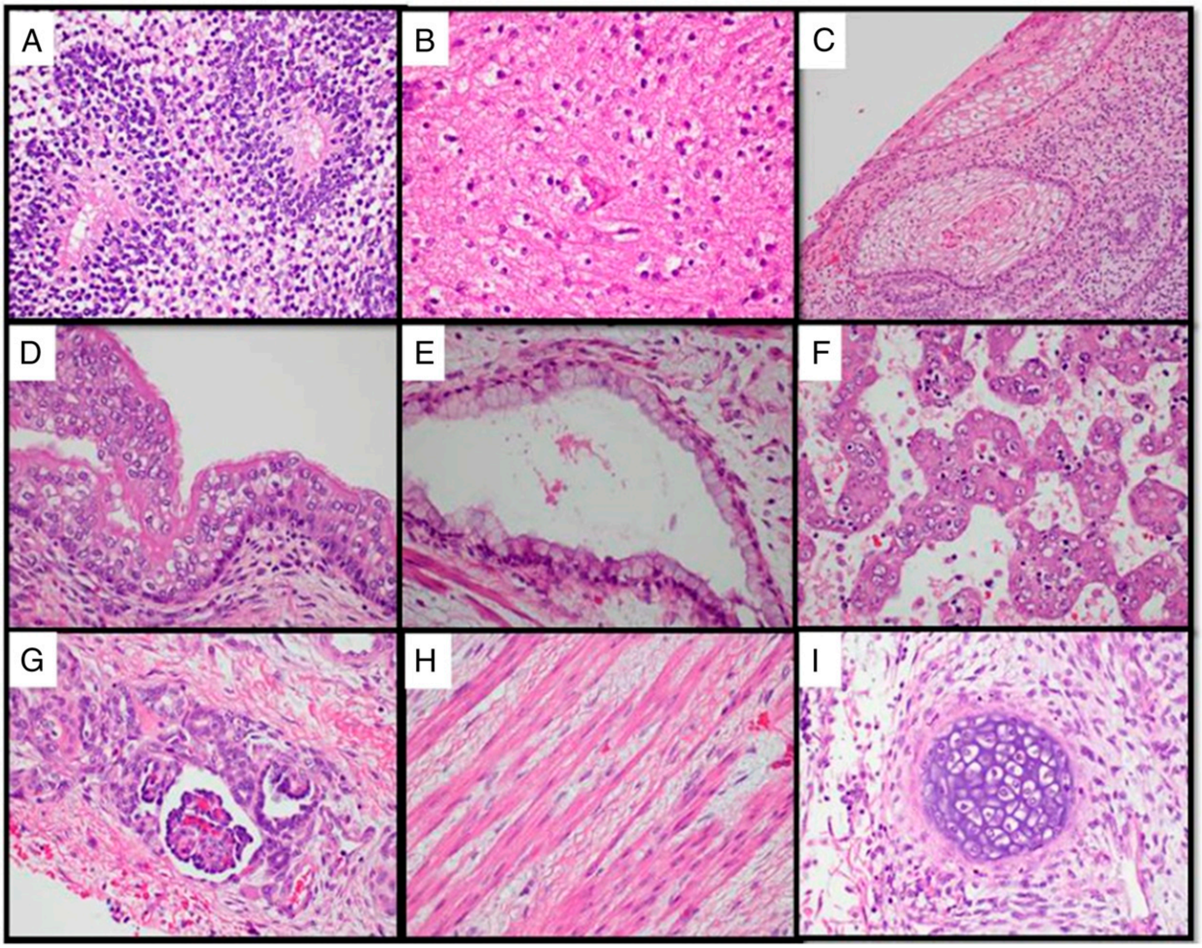

Figure 4. Pathology slides of the sacrococcygeal teratoma. A. Immature neuroepithelium, which defines the teratoma as immature. B. Brain tissue. C. Squamous epithelium. D. Ciliated (respiratory-type) epithelium. E. Mucous epithelium (goblet cells). F. Liver (cords of hepatocytes). G. Kidney (glomeruli and tubules). H. Smooth muscle. I. Cartilage. (All hematoxylin-eosin; ×400 original magnification.)

as improved differentiation and identification of the intrapelvic extension in the mass and any associated anomalies.

The differential diagnosis of SCT includes meningocele; for an anechoic mass, a meconial and mesenteric cyst, ovarian cyst, and hydrocolpos; and for a solid mass, a hemangioma, lipoma, malignant melanoma, and fetus in fetu.

The optimal strategy for managing pregnancies with large SCTs is an area of debate. For large high-risk SCTs, Roybal et al proposed an algorithm for the management of prenatal SCT (4). For fetuses with type I or II SCT, which develop early signs of fetal hydrops before 28 weeks, without signs of impending labor, severe placentomegaly, or maternal complications, fetal surgery is recommended. In patients with contraindications to fetal surgery (type III or IV SCT, cervical shortening) that develop fetal hydrops before 27 weeks, maternal health precedes any fetal intervention. Delivery by cesarean or ex utero intrapartum treatment procedure is recommended for fetuses between 27 and 32 weeks who have high-risk SCT or preterm labor but do not present with hydrops.

Fetal intervention is in the form of a debulking procedure, complete resection of the tumor, or radiofrequency ablation for high cardiac output failure cases.

Many studies have tried using different parameters to predict adverse outcomes in SCT cases. SCT growth rate greater than 61 cm^3 per week was associated with adverse outcomes including death, high output cardiac failure, and preterm delivery. A growth rate greater than 165 cm^3 per week was associated with death. Benachi et al, (5) in a retrospective review of the charts of 44 fetuses with SCTs, showed an association of tumor diameter greater than or equal to 10 cm, fast growth, and high cardiac output failure with higher perinatal morbidity and mortality. Sy et al (6) showed an association of a ratio of solid tumor volume to head volume greater than 1 or a rising ratio with ultrasonographic signs of decompensation, including hepatomegaly, placentomegaly, polyhydramnios, cardiomegaly, ascites, or pericardial effusion. The study also found that the rate of change in the ratio obtained from serial ultrasonography has higher potential to guide management.

At birth, a teratoma size can be large enough to account for 30% to 40% of the neonatal weight. In a retrospective cohort study (7) of 97 fetuses prenatally diagnosed with SCTs between 2000 and 2009, the overall mortality was 26%. The gestational age at delivery was less than 28 weeks in 5 cases, 28 to 31 weeks in 13 cases, 32 to 36 weeks in 27 cases, and more than 37 weeks in 37 cases. The tumor component was cystic in 54 cases and predominantly solid in 32 cases, with mortality rates of 2% and 33%, respectively.

Postnatally, in the absence of prenatal screening, SCT can be visible as a mass at birth. In most cases, neonates with SCT may not have symptoms, and neonatal intensive care may be needed for prematurity, disseminated intravascular coagulopathy, tumor rupture, or high cardiac output failure. The presence of intrapelvic extension may cause urinary obstruction symptoms. Hemorrhagic complications are the most common cause of neonatal mortality.

Postnatal management of an SCT is typically resection of the mass together with the coccyx. An abdominal-perineal approach is recommended for masses with pelvic extensions. Malignant SCTs have generally been treated with surgery and chemotherapy, though some series have suggested that surgery alone may be an option for early-stage malignant SCT. (8) The long-term survival for SCT resected soon after birth is 92% to 95%. (1)

Long-term follow-up of these patients with ultrasonography, serum markers, and physical examination is essential for detecting recurrences (10%–21%) as well as any long-term complications, including fecal or urinary incontinence. Follow-up should be performed every 2 to 3 months for 3 years.

Gabra et al identified 33 patients with SCT between 1977 and 2001. The sacral approach was used in 76% and a combined abdominal and sacral approach was used in 24%. Twenty patients had long-term follow-up, of which 25% reported constipation with soiling and 35% reported urinary incontinence. (9)

Risk factors for recurrence are malignant elements at resection margin, not removing the coccyx, and tumor spillage.

Recent studies have postulated that surgically excised SCTs can be a source for human embryonic stem cells.

Our case was unique given the lack of prenatal diagnosis, despite the large size of the tumor (probably due to rapid growth). It also highlights the importance of effective communication between multidisciplinary team members and the parents.

Follow-up

Despite the severity of illness and large volume of blood product transfusion before and at the time of surgery, MRI of the brain at discharge was normal. The patient was discharged at 38 weeks of age with follow-up with our pediatric oncology department. The patient's last AFP measurement at 7 months of age was 19.2 ng/mL (19.2 μg/L). There was no evidence of recurrent SCT on MRI 7 months after resection.

Lessons for the Clinician

- Despite advanced imaging studies, a sacrococcygeal teratoma (SCT) can still present as an undiagnosed prenatal mass.
- Prematurity can be a further complicating factor in cases of SCTs.
- An excellent multidisciplinary approach to complicated cases can be very effective in achieving desirable outcomes.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical and laboratory features and management of neonatal teratoma in the newborn.

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3 Term Neonate with Tachycardia

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AUTHOR DISCLOSURE Drs Daryani, Shaw, and Venkatnarayan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male infant is born at 39 weeks to a 27-year-old, gravida 3, para 1, blood group B–negative woman with an uneventful antenatal period and good antenatal care. The birth was via emergency lower-segment cesarean delivery, in view of breech presentation during labor and a birthweight of 3,100 g (appropriate for gestational age). The infant is born with no respiratory effort and bradycardia at birth requiring positive pressure ventilation. He is noticed to have micrognathia and glossoptosis causing airway obstruction and respiratory distress, with associated cleft palate (Figs 1 and 2), suggestive of Pierre Robin sequence. The infant's

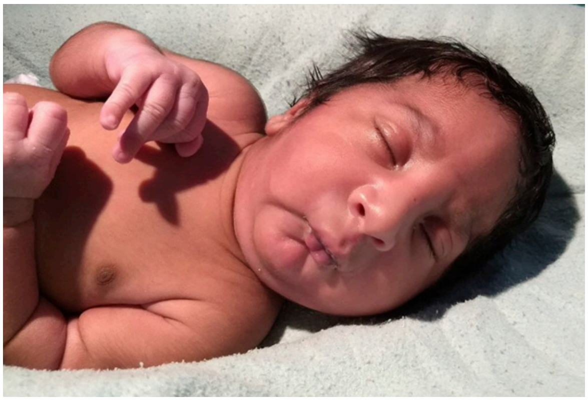


Figure 1. Micrognathia.

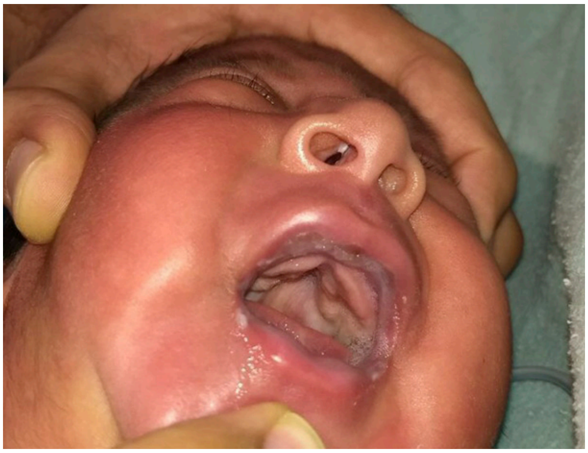


Figure 2. U-shaped cleft palate.

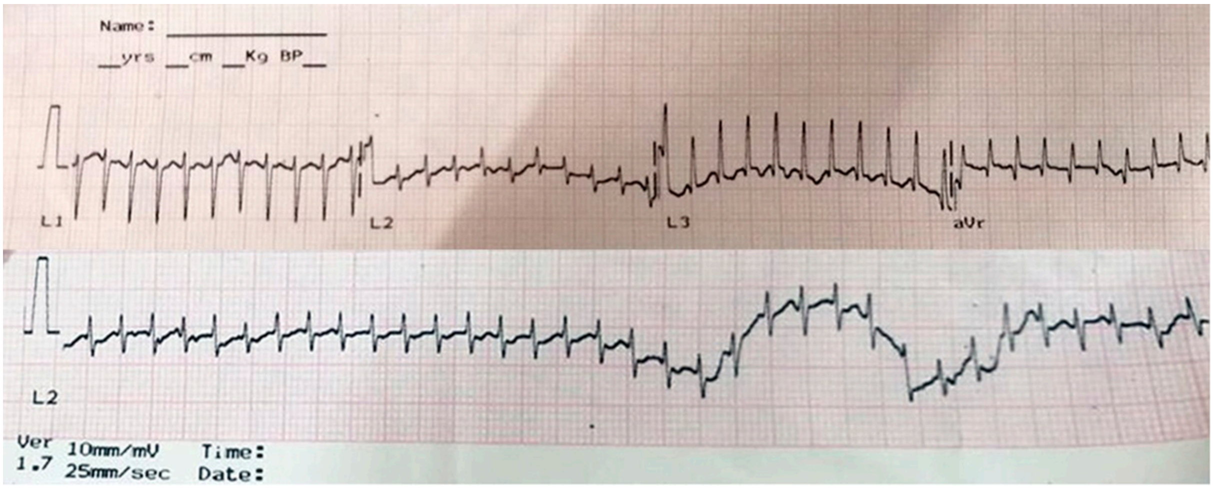


Figure 3. Supraventricular tachycardia.

1-minute Apgar score is 4, and he develops stridor and respiratory distress soon after birth. A nasopharyngeal airway is inserted to relieve the respiratory distress. His 5-minute Apgar score improves to 7, and he is moved to the NICU for observation. He has no other obvious congenital anomaly. His chest radiograph is essentially normal. Approximately 1 hour after birth, he starts having tachycardia, with a heart rate of about 250 beats/minute, and showing features of supraventricular tachycardia on electrocardiography (Fig 3). Adenosine is injected at 100 μg/kg under cardiac monitoring to terminate the arrhythmia.

DISCUSSION

Progression

At 10 and 11$^1/_2$ hours after birth, the infant started having tachycardia again, with a heart rate in the range of 200 to 250 beats/min, and adenosine was injected each time to terminate the arrhythmia. His serum electrolytes and calcium were normal, with serum sodium 140 mEq/L (140 mmol/L; normal range, 133–142 mEq/L [133–142 mmol/L]), serum potassium 3.6 mEq/L (3.6 mmol/L; normal range, 3.5–5.0 mEq/L [3.5–5.0 mmol/L]), and serum calcium 9.8 mg/dL (2.4 mmol/L; 8.0–10.7 mg/dL [2–2.6 mmol/L]). Echocardiography revealed a normal structure except for a 2-mm patent ductus arteriosus with left to right shunt (hemodynamically insignificant). The infant was started on amiodarone treatment (loading dose 5 mg/kg, followed by maintenance infusion and switched to oral therapy on day 3) to prevent further episodes of supraventricular tachycardia. Findings on postarrhythmia termination electrocardiography were suggestive of atrioventricular reentry tachycardia in the form of discernible P waves, RP interval greater than 100 milliseconds, and ST segment depression with absence of δ waves (Fig 4).

Diagnosis/Management

The infant's mother and sibling (5-year-old sister) also have mild mandibular hypoplasia but with no associated cleft palate, glossoptosis, or arrhythmia.

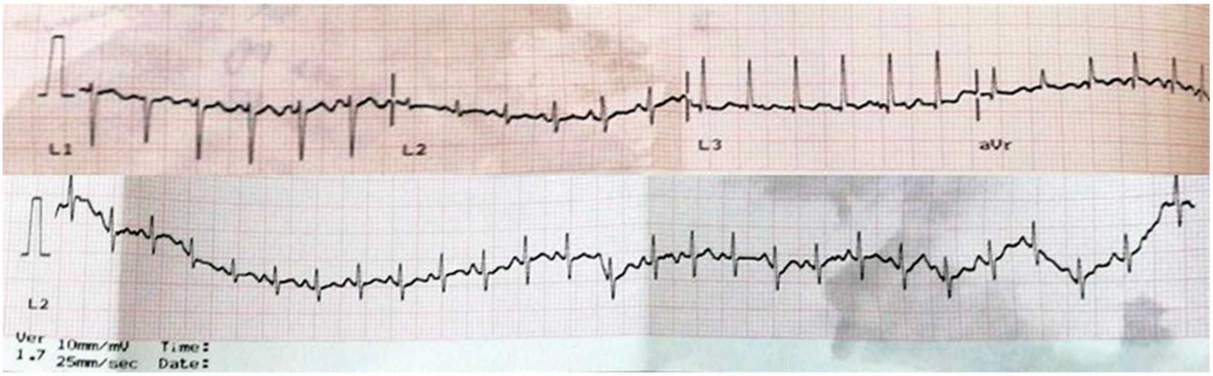
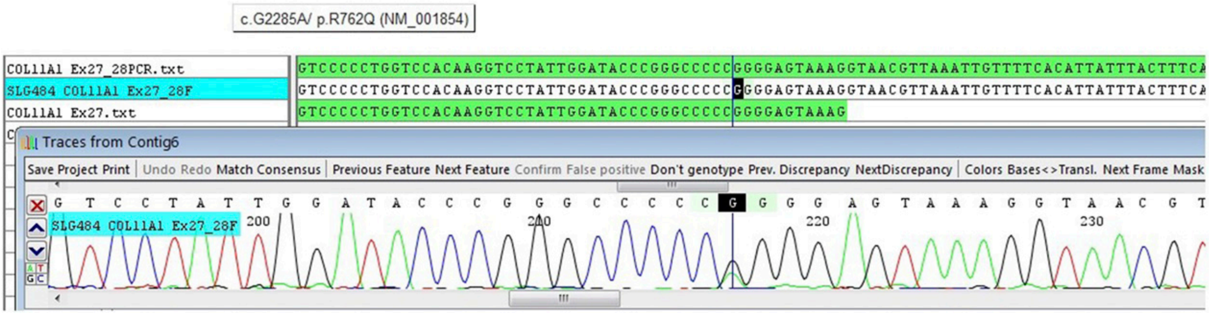


Figure 4. Postadenosine rhythm suggestive of atrioventricular reentry tachycardia.



c.G2285A/ p.R762Q (NM_001854)

```
COL11A1 Ex27_28PCR.txt   GTCCCCCTGGTCCACAAGGTCCTATTGGATACCCGGGCCCCCGGGGAGTAAAGGTAACGTTAAATTGTTTTCACATTATTTACTTTCA
SLG484 COL11A1 Ex27_28F  GTCCCCCTGGTCCACAAGGTCCTATTGGATACCCGGGCCCCCGGGGAGTAAAGGTAACGTTAAATTGTTTTCACATTATTTACTTTCA
COL11A1 Ex27.txt         GTCCCCCTGGTCCACAAGGTCCTATTGGATACCCGGGCCCCCGGGGAGTAAAG
```

Traces from Contig6
Save Project Print
Undo Redo Match Consensus
Previous Feature Next Feature Confirm False positive Don't genotype Prev. Discrepancy NextDiscrepancy
Colors Bases<>Transl. Next Frame Mask
G T C C T A T T G G A T A C C C G G G C C C C C G G G A G T A A A G G T A A C G T
SLG484 COL11A1 Ex27_28F
200
210
220
230

Figure 5. Missense mutation of *COL11A1*.

The clinical exome sequencing performed to rule out genetic association revealed autosomal dominant heterozygous missense mutation of the *COL11A1* (chr 1:103461555) and *SOX9* (chr 17: 70119716) genes (Fig 5). In view of the possibilities of associated campomelic dysplasia (*SOX9*) and Stickler or Marshall syndrome (*COL11A1*), a hearing evaluation and eye examination were performed, results of which were normal.

At 1 month of age, the infant underwent elective mandibular distraction in view of airway compromise. On follow-up, at 3 months of age, he was doing well, with no features of airway obstruction and no recurrence of arrhythmia.

THE CONDITION

Pierre Robin sequence (PRS) is a congenital abnormality characterized by micrognathia and glossoptosis, with or without cleft palate, leading to life-threatening respiratory obstruction and feeding difficulties during the neonatal period. (1)

PRS was named after the French stomatologist who, in 1923 and 1934, described the problems associated with newborn micrognathia. Its incidence is estimated to be around 1 in 8,500 to 14,000, (2)(3) but the variability of diagnostic criteria makes it difficult to define precisely.

PRS has been associated with a range of syndromes and chromosomal anomalies, but the underlying pathogenesis of PRS is yet to be fully elucidated. Hypothesized models include a primary failure of mandibular outgrowth or a muscular defect with failure of tongue descent.

More than 40 syndromes with PRS have been described, the most common of which are Stickler syndrome and 22q11.2 deletion syndrome. (4) Stickler syndrome type II is caused by heterozygous mutation in the *COL11A1* gene, found on 1p21 chromosome. Marshall disorder is a similar disorder with respect to phenotype and genotype. The *SOX9* gene has also been associated with isolated PRS.

Cardiac arrhythmia in PRS has been described with Andersen-Tawil syndrome (associated with long QT syndrome; *KCNJ2* mutation) (1) and in association with *BMP2* gene deletion (associated with Wolff-Parkinson-White syndrome). (5)(6)(7)

Lessons for the Clinician

- Pierre Robin sequence is a craniofacial anomaly presenting with varying degrees of micrognathia, cleft palate, and glossoptosis leading to mild breathing difficulty to life-threatening obstructive apnea and feeding difficulties during the neonatal period.
- It may present as an isolated anomaly or part of myriad chromosomal anomalies and syndromes.
- Supraventricular tachycardia is a rare association with Pierre Robin sequence.
- High index of suspicion is required to detect possible pathologic tachycardia in neonates.

ACKNOWLEDGMENT

We acknowledge the contributions of Dr H Ravi Ramamurthy, expert in pediatric cardiology, in the management of this case.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the associations and clinical features and management of macroglossia and hypoplastic mandible, including the Pierre Robin syndrome.

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ANSWER KEY FOR JULY 2018 NEOREVIEWS

Acyanotic Congenital Heart Disease: Left-to-Right Shunt Lesions 1. C; 2. D; 3. A; 4. B; 5. C.

Right and Left Ventricular Outflow Tract Obstructive Lesions: 1. A; 2. E; 3. B; 4. D; 5. A.

Case 3: Term Neonate with Tachycardia

Hitesh Daryani, Subhash Chandra Shaw and Kannan Venkatnarayan

NeoReviews 2018;19;e418
DOI: 10.1542/neo.19-7-e418

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Was This Case of Necrotizing Enterocolitis Preventable?

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AUTHOR DISCLOSURE Dr Sims has disclosed that she has been compensated for reviewing records and providing testimony in some of the cases highlighted in Legal Briefs. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A 28 1/7 week gestational age male infant with a birthweight of 1,280 g was born to a 23-year- old gravida 3, para 0-0-2-0 woman. The pregnancy was uneventful until the night before delivery when she developed preterm labor. She received 1 dose of betamethasone 8 hours before delivery. She also received 3 doses of penicillin for unknown group B *Streptococcus* status. Artificial rupture of membranes occurred a few hours before birth and the amniotic fluid was clear. The birth was via normal spontaneous vaginal delivery. The placenta appeared grossly normal, but subsequent pathologic examination showed mild chorioamnionitis. The infant's Apgar scores were 8 at 1 minute and 9 at 5 minutes of age. The infant was clinically stable and treated with continuous positive airway pressure. The infant had a normal complete blood cell (CBC) count and was started on antibiotics because of preterm labor. The infant also received intravenous fluids at 80 mL/kg per day. On day 1, caffeine was initiated and phototherapy was started because the infant's bilirubin was 8.1 mg/dL (138.5 μmol/L). At that time, the infant's weight was down 11% from birthweight. On day 2, a percutaneous intravenous central catheter (PICC) was placed.

On day 3, the infant's weight loss was down 13% from birthweight and his sodium was 151 mEq/L (151 mmol/L) with a blood urea nitrogen of 30 mg/dL (10.7 mmol/L). The infant was started on trophic breast milk feedings of 1.5 mL every 3 hours. With the intravenous fluids being infused at 122 mL/kg per day, the total volume of fluids was 154 mL/kg per day. The infant did not receive probiotics. As the feedings increased, the volume infused diminished. ***The plaintiff neonatologist thought that the infant should have had his hydration status better managed to prevent dehydration and that it was inappropriate to provide feedings during this dehydration.*** On day 4, the infant's weight was down 14% from birthweight and the feedings were increased to 4 mL every 3 hours. The nurse documented multiple residuals of 1 mL. ***The plaintiff neonatologist was critical of feeding the infant with such a weight loss because the infant's hydration status was not improving.*** On day 6, the infant's weight was down 16% from birthweight and visible abdominal loops were appreciated. The infant's feedings were increased to 5 mL every 3 hours. ***On deposition, the treating physician explained that hydration was being addressed by increasing the volume of feedings. The plaintiff neonatologist was critical of increasing the infant's feedings in the presence of dehydration and visible abdominal loops. The defense team claimed that it was standard of care to increase this infant's feedings and that the loops were intermittent and not concerning.*** On days 7 to 9, despite the new clinical finding of multiple bradycardias, desaturations, and color changes, feeding volumes were increased to 9 mL, then to 12 mL, and finally to 15 mL. During this time, the total intake of volume was 136 mL/kg per day, with parenteral infusions providing 60 mL/kg per day and the enteral route provided 76 mL/kg per day. The infant's weight normalized and the serum sodium became normal. Caffeine was discontinued. The abdominal girth increased by 2 cm during this period. More nonbilious residuals were apparent and these ranged from 1 mL to 8 mL. The infant was able to pass stools appropriately. ***The defense team and treating clinicians stated that residuals could be ignored in this infant because of well-appearing status and that the infant's nutrition was the top priority.*** At day 10, abdominal distention and visible loops reappeared. ***The plaintiff neonatologist stated that the infant was exhibiting signs of feeding intolerance. The defense disagreed.*** The feedings continued with exclusive breast milk, but were now fortified to 22 calories/oz.

Over the next week (days 11–19), feedings increased to 27 mL, and the caloric density was advanced to 27 calories/oz by adding a 30-calorie/oz formula to the breast milk and human milk fortifier. ***The plaintiff neonatologist was critical of the increase in the osmolality of the feedings.*** The infant's bradycardia and desaturation became more severe. The infant's abdominal girth was increased by another 3 cm, but the abdomen remained soft. ***The defense team stated that because the infant's abdomen was soft it was safe to feed the infant. The plaintiff disagreed and pointed out that premature infants have decreased tone, including the abdominal tone, making the abdominal girth an unreliable sign.*** In an attempt to ameliorate the bradycardia and desaturations, the duration of the infant's feedings was increased to 1 hour. ***The plaintiff neonatologist explained that the human gastrointestinal tract is designed for alternating feed-fast cycles and was not adapted for tolerating a continuous flow of nutrients. The plaintiff team criticized this team's "relentless" approach to feedings and the infant's bradycardia and desaturation were a result of the "reckless" feeding pace.***

The infant's PICC was discontinued on day 13. This now allowed his transfer from the NICU to the growing premature nursery where the nurse-to-infant ratio was 1:3. ***The plaintiff neonatologist was critical of the removal of the PICC because the infant should have continued to receive intravenous fluids with less enteral volume. Furthermore, the plaintiff team felt that this infant exhibited several red flags that should have prompted more experienced nursing than the nursery could provide. The defense explained that removal of central lines is very important to reduce the risk of central line–associated bacterial infections, a goal for all NICU patients.***

By day 20, the infant began having small nonbilious emesis. The infant's desaturation was more prolonged and the infant's color changes were more pronounced. His abdominal girth was increased an additional 1 cm. Because of an excessive weight gain, the 27-calorie/oz formula was reduced to 24 calories/oz, but the volume of feedings was increased another 2 mL every 3 hours. Because the bradycardia and desaturation continued to be severe on day 22, caffeine was restarted, a CBC count was evaluated, and the infant's hematocrit was found to be 21% (no reticulocyte sent), which prompted a transfusion of packed red blood cells over 4 hours. By day 24, the infant's feedings were at 33 mL every 3 hours and he received another transfusion for persistent anemia. The infant appeared jaundiced and a bilirubin of 22.3 mg/dL (381.4 μmol/L) with a direct component of 1.6 mg/dL (27.3 μmol/L) was found. He had poor perfusion. He developed temperature instability and continued to have multiple desaturations. After sending a blood sample for a CBC count and culture, the medical team started him on amikacin and vancomycin. At this point, the infant was placed on nil per os (NPO) status to perform a double volume exchange transfusion. The infant tolerated the procedure. The white blood cell count, differential, and platelet count were benign and the blood culture was negative. He was evaluated for possible glucose-6-phosphate dehydrogenase deficiency, which was repeated after discharge. Hematology concluded that the infant did not have this diagnosis. ***The plaintiff neonatologist pointed out that the most likely reason for the infant's hyperbilirubinemia was an ileus with possible transient seeding of organisms from the gastrointestinal tract (translocation).***

Six hours after the exchange transfusion, the infant's feedings were restarted at 33 mL every 3 hours. The infant's abdominal girth increased by 2 cm and the glucose concentration was 261 mg/dL (14.5 mmol/L). ***The plaintiff neonatologist was critical that an evaluation was not performed to understand these findings.*** On day 25, the infant had large nonbilious emesis. The infant developed unstable temperatures, persistent tachycardia, multiple desaturations, and lethargy. His abdomen was noted to be distended and firm with absent bowel sounds. At this point, he was again placed on NPO status and a Replogle tube was placed. ***The plaintiff neonatologist was critical that it took this extent of deterioration for the staff to place the infant on NPO status.*** A blood gas measurement showed a pH of 7.04, a partial pressure of carbon dioxide of 16 mm Hg (2.1 kPa), and a profound metabolic acidosis. His white blood cell count was $1.5\times10^3/\mu L$ ($1.5\times10^9/L$) and a second blood specimen was sent for culture and subsequently reported to be negative. Upper gastrointestinal tract radiography was ordered. ***The plaintiff neonatologist was critical of this order, explaining that it was not only unnecessary but dangerous.*** Because the infant was so unstable, it was not performed. At this point, the infant was transferred to the NICU and the neonatologist consulted the surgical team. ***The plaintiff neonatologist was again critical that the team had not transferred the patient to the NICU sooner, where there was a better nursing-to-patient ratio and more experienced nurses. He was further critical that abdominal radiography and a surgical consultation were not conducted earlier in the course, on day 24 at least.*** Abdominal radiography showed dilated bowel loops, but no free air. A PICC was placed and dopamine was initiated for blood pressure support. Erythema was present on the infant's abdomen by the following morning. By late afternoon, the infant was taken to the operating room where necrosis of 40% of his cecum and a large perforation in the first part of the large colon was found with multiple layers of adhesions. ***The defense neonatologist claimed that all the feedings met the standard of care. He explained that the infant's necrotizing enterocolitis (NEC) was most likely from the packed red blood cell transfusion given during feedings, a concept known to increase the risk for NEC. Moreover, the defense pointed out that, had it been known at that time, the packed red blood transfusion would not have been given. The plaintiff neonatologist pointed out that the association with packed red blood cells and NEC has not been shown to be valid. The defense neonatologist also said that the mother's chorioamnionitis was a big risk for the infant's development of NEC. The plaintiff pointed out that this was not true either, with upward of 70% of premature infants being born to women with either clinical or histologic chorioamnionitis; moreover, the connection between chorioamnionitis and NEC has not been shown despite numerous studies.***

The infant had several subsequent surgeries secondary to adhesions and reperforations. He was discharged at 4 months of age with serious malabsorption issues and hypertension. After discharge, he was admitted many times for various bowel surgeries and complications that included *Pseudomonas* and *Enterococcus* peritonitis. ***The plaintiff neonatologist pointed out that repeated exposure to anesthesia and surgery before the age of 2 years was a significant independent risk factor for neurodevelopmental problems.*** On follow-up, the infant had short gut and malabsorption issues, developmental delays, and hypertension. The case was settled without going to trial.

DISCUSSION

NEC is a disorder manifested by ischemic necrosis of the intestinal mucosa. It is characterized by inflammation, invasion of enteric gas-forming organisms, and dissection of gas into the muscularis and portal venous system. Depending on the progression of the disease and the presence of underlying pathogenic factors, it may move into gangrenous necrosis and perforation. As the intestine heals, bowel wall thickening, fibrinous adhesions, and areas of stenosis appear. NEC occurs in 1 to 3 per 1,000 live births, with an incidence of 6% to 7% in infants with birthweights less than 1,500 g. Intestinal immaturity, aggressive feedings, and inflammatory response to interactions between intestinal epithelial barrier and luminal microbes are key contributors to the development of NEC in the preterm infant. The pathophysiologic mechanisms of the development of NEC in premature infants are summarized as follows:

- Intestinal immaturity
  - Impaired mucosal defense of the immature intestine
  - Increased permeability of the immature intestine
  - Bacterial penetration into the intestinal wall (translocation) of the immature intestine
  - Decreased bowel motility resulting in delayed transit time, which increases bacterial proliferation and overgrowth in the immature intestine
  - Excessive inflammatory response to luminal microbial stimuli altering protective barriers in the intestine
  - Dysbiosis
- Feedings
  - Human milk does offer some protective effect compared with commercial formulas
  - More than 90% of preterm infants who develop NEC were fed
  - Both human milk and commercial formulas serve as substrates for bacterial proliferation in the gut
  - Inability of preterm infants to completely digest and absorb nutrients results in bacterial fermentation that may cause mucosal injury
  - Delayed transit time and leaky gut epithelium in the premature infant predispose the gastrointestinal tract to damage
  - Hyperosmolar formulas and oral medications have hypertonic additives that irritate the intestinal mucosa (eg, theophylline and phenobarbital)
- Circulatory instability or hypoxia of the gastrointestinal tract
  - Subtle reduction of blood flow and subsequent reperfusion in response to hypoxia
  - Hypoxia and ischemia modulate the balance in microvascular tone which probably play a downstream role in the pathogenic cascade that leads to NEC
  - Cocaine exposure
  - Significant anemia

Other emerging associations with NEC include magnesium or copper deficiency, perhaps through a mechanism affecting cytokines or oxygen-free radicals. Also, drugs that inhibit histamine at the H2 receptors (eg, cimetidine, ranitidine, and famotidine), thereby inhibiting gastric acid secretion, may increase the risk of NEC. This mechanism is thought to result from a reduction in gastric acidity, facilitating bacterial growth and thereby increasing NEC risk. In term infants, NEC is commonly associated with congenital heart disease (such as hypoplastic left heart syndrome and coarctation of the aorta) that results in intestinal hypoxia and/or hypoperfusion.

In addition, infants with intrauterine growth restriction, asphyxia, polycythemia/hyperviscosity, and those that require exchange transfusions are at increased risk for NEC.

Although the mature infant determines the volume of feedings through nipple-feeding, premature infants born at less than 34 weeks' gestation depend on health care clinicians to determine the volume and advancement of feedings that are introduced by gavage. Feeding protocols do not substitute for thoughtful clinical involvement with vigilance paid to each and every clinical sign of the premature infant. Physicians need to be very mindful that tolerance to volumes introduced into the gastrointestinal tract need to be very individualized. Although more protective than formula feedings, human milk feedings do not obviate the vulnerability of the premature intestinal tract.

In patients affected by NEC, sometimes multiple etiologic factors affect the development of this disease. There are undoubtedly many risk factors that clinicians cannot control currently, such as intestinal immaturity and inflammatory response to interactions between intestinal epithelial barrier and luminal microbes. However, we can control what and how much is introduced into the gastrointestinal system and be vigilant of the infant's clinical signs. Future promising directions include: 1) a probiotic supplement that could be given to pregnant women or premature infants along with human breast milk, which will bolster the immune system of premature infants to combat the inflammatory response; 2) identification of various predictive and diagnostic biomarkers; and 3) establishment of a national biorepository and registry to support future investigation dedicated to better understanding NEC.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical and diagnostic features, evaluation, management, and complications of NEC.

Suggested Readings

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Legal Briefs: Was This Case of Necrotizing Enterocolitis Preventable?

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Recurrent Variable Decelerations in a Woman with Trial of Labor after Cesarean

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate

AUTHOR DISCLOSURE Drs Demasio and Kuba have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. **Arterial Umbilical Cord Gas Values**

	pH	Pco_2 (mm Hg)	Po_2 (mm Hg)	Base Excess
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤−10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤−10
Metabolic acidosis	<7.20	<60	Variable	≥−10
Mixed acidosis	<7.20	>60	Variable	≥−10

*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695.

- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable
Minimal: Amplitude range is greater than undetectable to 5 beats/min
Moderate: Amplitude range is 6–25 beats/min
Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
    - Normal: ≤5 contractions in 10 minutes
    - Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline
- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - ■ Recurrent late decelerations
    - ■ Recurrent variable decelerations
    - ■ Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008; 112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

History

A 32-year-old gravida 2, para 1-0-0-1 pregnant woman presented to the labor and delivery triage at 40-4/7 weeks' gestation with contractions. She had planned for a trial of labor after cesarean (TOLAC) because of a prior elective, term cesarean delivery that was performed in the Dominican Republic. At that time, the cesarean had been recommended by her obstetric provider because of her hepatitis B carrier status. The operative report was not available. For this pregnancy, the patient desired a TOLAC and had been counseled about the risks and benefits before arriving at the labor and delivery department. The FHR tracing was reassuring and is shown in Fig 1.

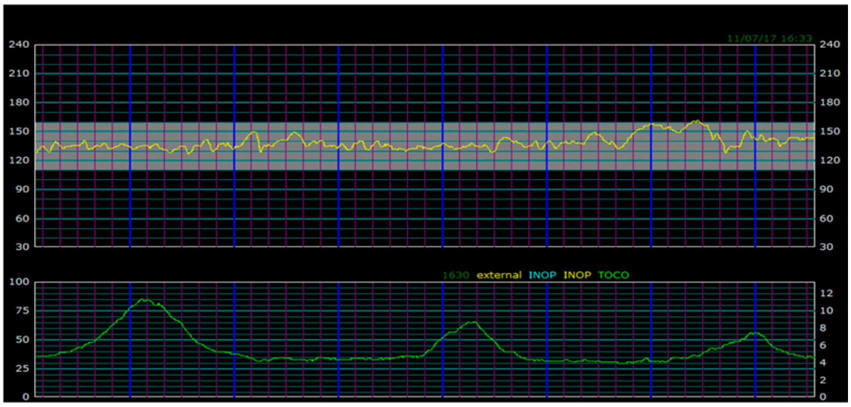

Figure 1. Electronic fetal monitoring strip 1.

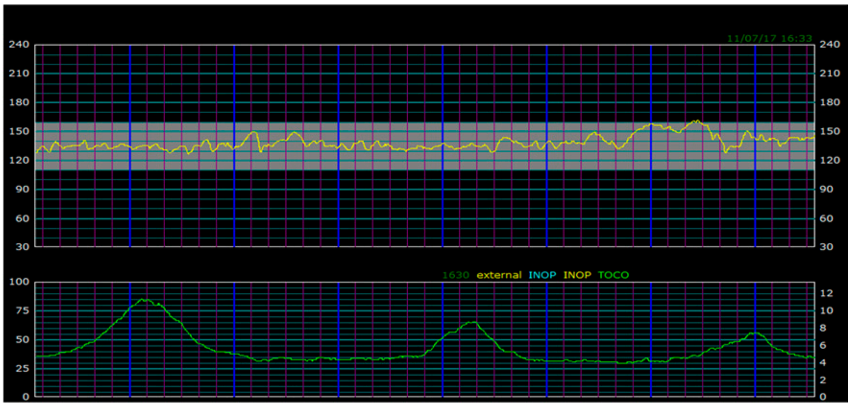

Figure 1. Electronic fetal monitoring strip 1.

Findings from EFM strip 1 are as follows:

- Baseline rate: 135 beats/min
- Baseline variability: Moderate
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: Every 4 minutes
- Interpretation: Category I
- Differential diagnosis: Reactive and reassuring FHR tracing
- Action: Expectant management

The woman's medical history was significant for a late start of prenatal care at 19 to 20 weeks' gestation, and consisted of a total of 11 prenatal visits. As mentioned earlier, she was previously diagnosed as positive for hepatitis B carrier status, and the viral load in this pregnancy was undetectable. All laboratory values were otherwise within normal limits and her third trimester group B *Streptococcus* culture was negative. Her prenatal course was uncomplicated, and her only medication was prenatal vitamins. Ultrasound examination 3 days before the present admission demonstrated an appropriately grown fetus with an estimated weight of 3,744 g.

On admission, an examination revealed a blood pressure of 118/77 mm Hg, pulse rate of 86 beats/min, no fever, and body mass index of 29 kg/m^2. Her cervix was 2-cm dilated, 70% effaced, and the vertex was at −3 station. The maternal pelvis was assessed to be adequate for vaginal delivery. The patient was uncomfortable with contractions, and was thought to be in early labor. She was admitted for expectant management and pain control. Admission laboratory values were within normal limits. She requested epidural analgesia, which was administered shortly after arrival at the labor room. Reexamination of the cervix after epidural initiation demonstrated further dilation to 4 cm, 80% effacement, −3 station, and a reassuring category II FHR tracing. She continued to labor, and around 6 hours after admission there was concern for the FHR tracing that demonstrated minimal variability and subtle decelerations (Fig 2). Intrauterine resuscitative measures were undertaken. The FHR tracing responded to these measures and a category I tracing was again noted. The clinicians were reassured by a positive result on a scalp stimulation test, which indicated a nonacidotic fetal pH.

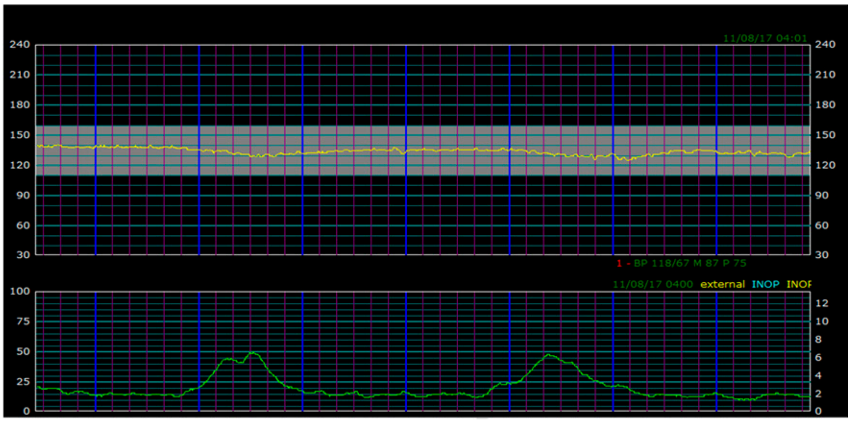

Figure 2. Electronic fetal monitoring strip 2.

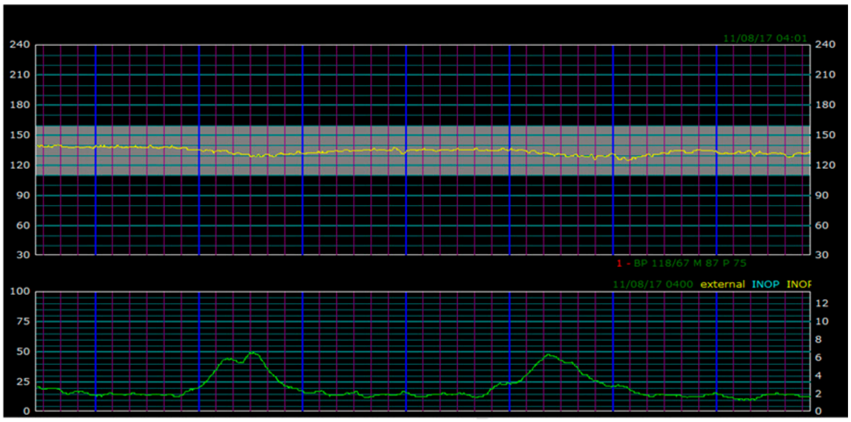

Figure 2. Electronic fetal monitoring strip 2.

Findings from EFM strip 2 are as follows:

- Baseline rate: 135 beats/min
- Baseline variability: Minimum
- Episodic patterns: None
- Periodic patterns: Late decelerations
- Uterine contractions: Every 3 minutes
- Interpretation: Category II
- Differential diagnosis: Recurrent late decelerations
- Action: Intrauterine resuscitation

Seven hours after admission, oxytocin augmentation was initiated, and soon afterwards, recurrent variable decelerations were seen (Fig 3). Amniotomy was performed and no amniotic fluid was observed. The cervix at this point was 5-cm dilated, 80% effaced, and at −1 station. Intrauterine resuscitation continued with an intravenous fluid bolus of normal saline, oxygen delivery, and repositioning. A category II tracing was obtained in which the baseline had minimal variability but with accelerations. Repeat cervix examination 30 minutes after the last examination revealed a change to 6 cm, 90% effacement, 0 station, indicating that the patient was actively laboring. Within a few minutes, the FHR tracing again developed into a pattern of recurrent decelerations (Fig 4) and an intrauterine pressure catheter was placed for planned amnioinfusion. Amnioinfusion was initiated and resolved the recurrent decelerations, restoring a category I FHR tracing pattern. Two hours after the last vaginal examination, labor was progressing and the cervix was found to be 8-cm dilated, 100% effaced, and the vertex descended to 0 station. She continued to labor without the use of oxytocin.

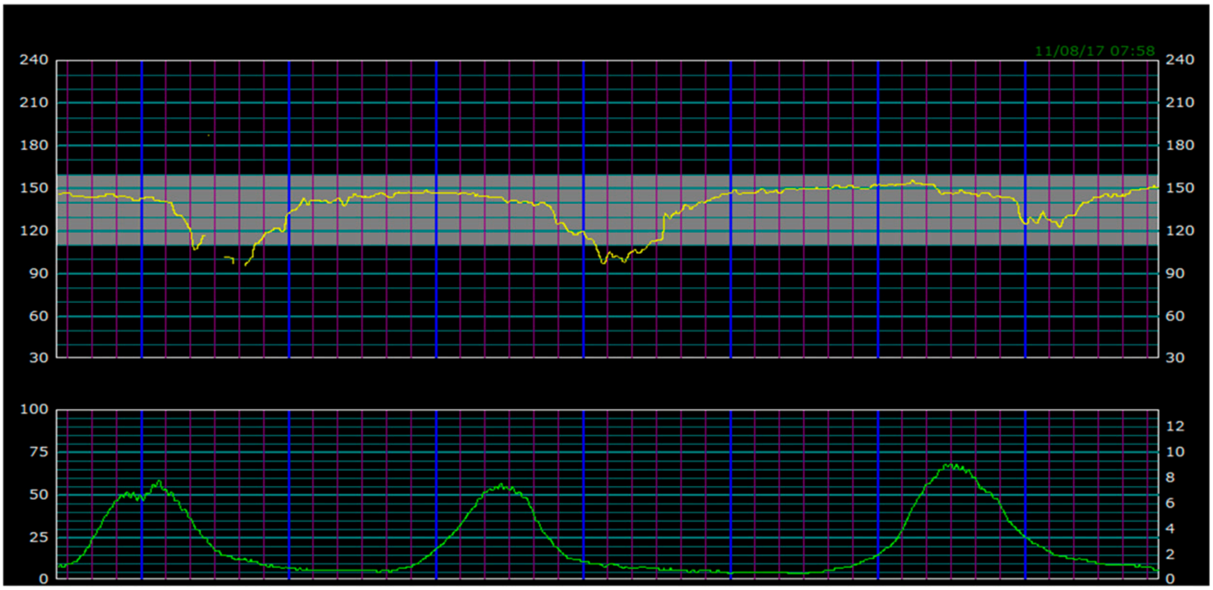

Figure 3. Electronic fetal monitoring strip 3.

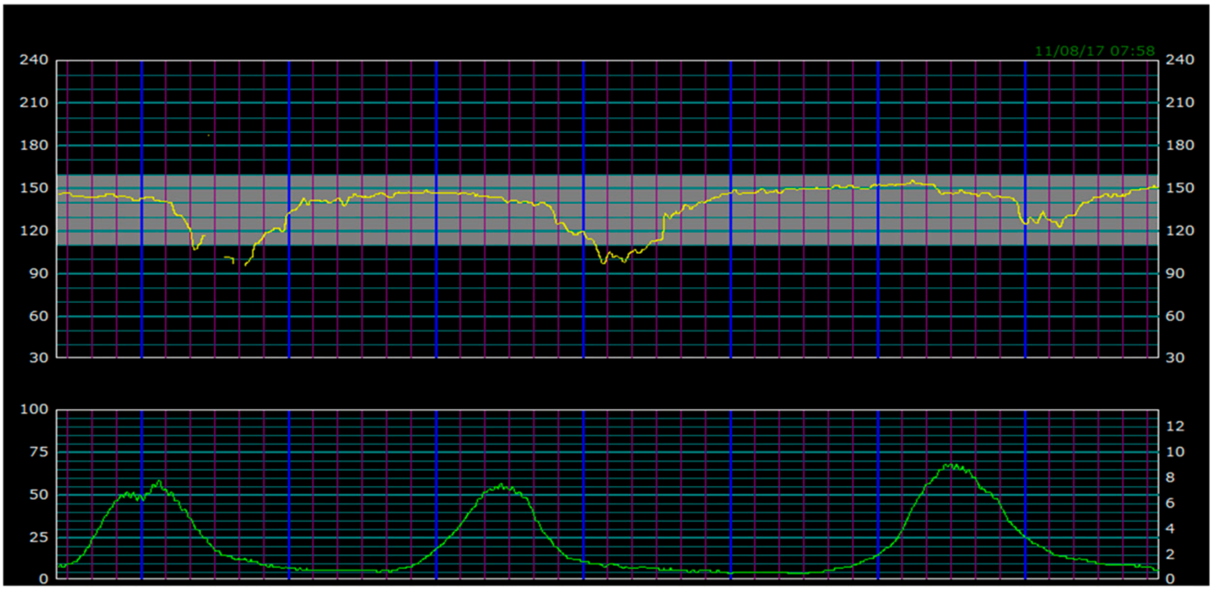

Figure 3. Electronic fetal monitoring strip 3.

Findings from EFM strip 3 are as follows:

- Baseline rate: 145 beats/min
- Baseline variability: Minimum variability
- Episodic patterns: None
- Periodic patterns: Recurrent variable decelerations
- Uterine contractions: Every 3 minutes
- Interpretation: Category II
- Differential diagnosis: Recurrent variable decelerations
- Action: Intrauterine resuscitation, amniotomy

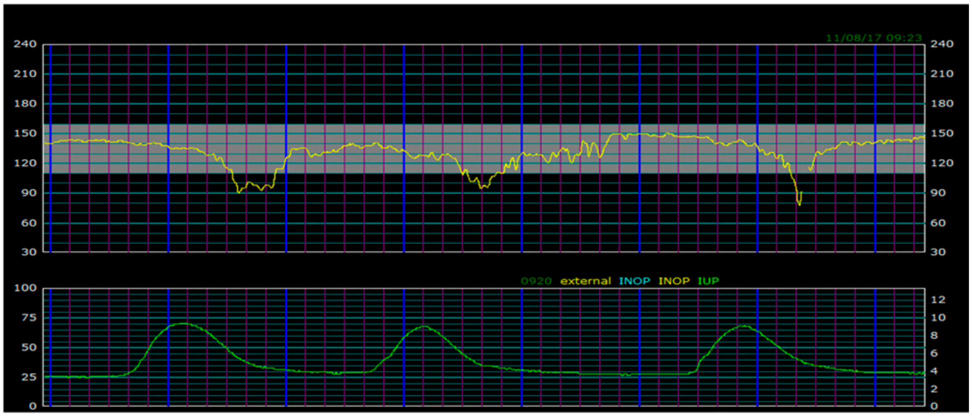

Figure 4. Electronic fetal monitoring strip 4.

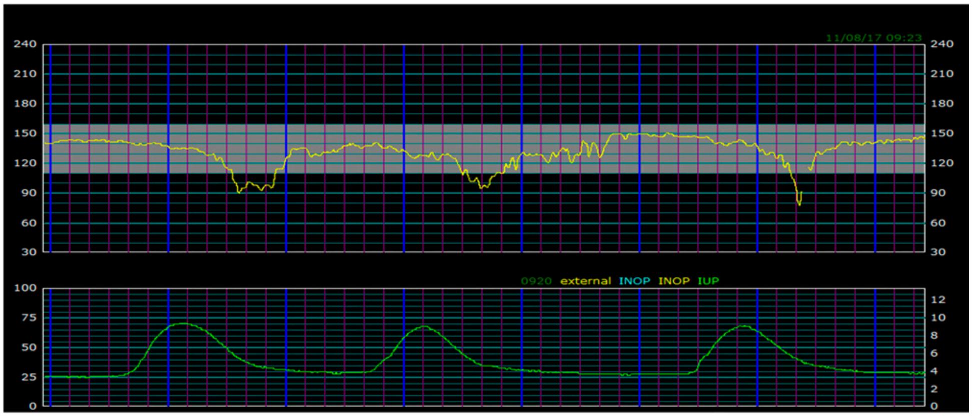

Figure 4. Electronic fetal monitoring strip 4.

Findings from EFM strip 4 are as follows:

- Baseline rate: 140 beats/min
- Baseline variability: Minimum variability
- Episodic patterns: None
- Periodic patterns: Recurrent variable decelerations
- Uterine contractions: Every 2 to 3 minutes
- Interpretation: Category II
- Differential diagnosis: Variable decelerations
- Action: Intrauterine amnioinfusion

One hour later, the tracing returned to a concerning category II tracing characterized by minimal variability and late decelerations (Fig 5). The clinicians interpreted the FHR tracing as category II, rather than category III, because of the presence of minimum variability rather than absent variability. They avoided placement of a fetal scalp electrode because of the hepatitis B carrier status. Cervical examination showed that only a rim of cervix remained. The effacement was 100% and station was +1, so the managing team believed the labor was progressing toward a vaginal delivery and were reassured by the descent of the presenting part. The labor continued to be closely observed. Within an hour, a category I FHR tracing was again noted, reassuring the managing team that the fetal pH was nonacidotic. One and a half hours later, she was completely dilated, 10 cm, 100% effaced, and at +1 station; maternal pushing efforts initiated the second stage of labor.

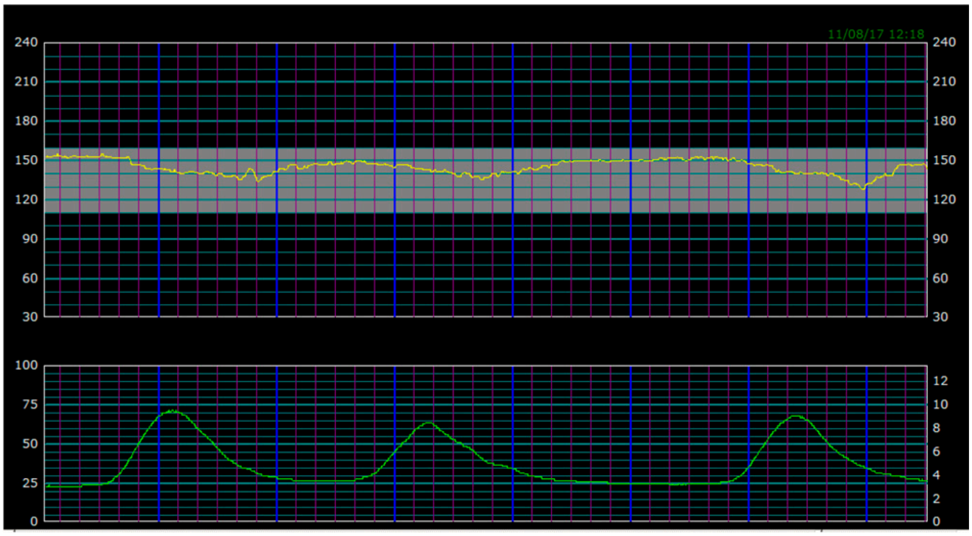

Figure 5. Electronic fetal monitoring strip 5.

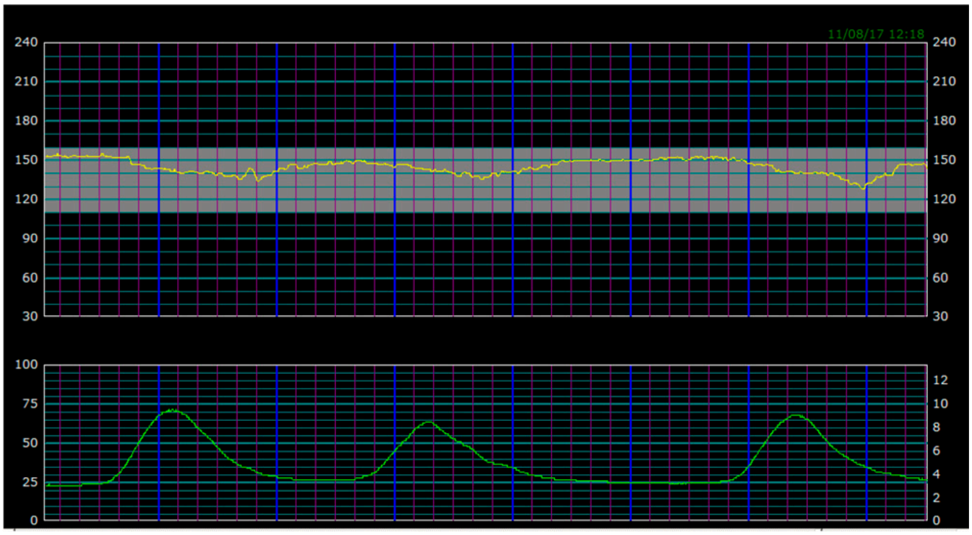

Figure 5. Electronic fetal monitoring strip 5.

Findings from EFM strip 5 are as follows:

- Baseline rate: 150 beats/min
- Baseline variability: Minimum variability
- Episodic patterns: None
- Periodic patterns: Recurrent late decelerations
- Uterine contractions: Every 2 to 3 minutes
- Interpretation: Category II
- Differential diagnosis: decelerations
- Action: Position change, intrauterine resuscitation

The second stage of labor was challenged by deep variable decelerations as noted in Fig 6. The variable deceleration pattern occurred with every contraction as she pushed for half an hour, but when not pushing, the FHR baseline showed tachycardia at 175 beats/min (Fig 7). Once a +2 station was achieved, delivery was expedited with a low forceps-assisted vaginal birth after cesarean.

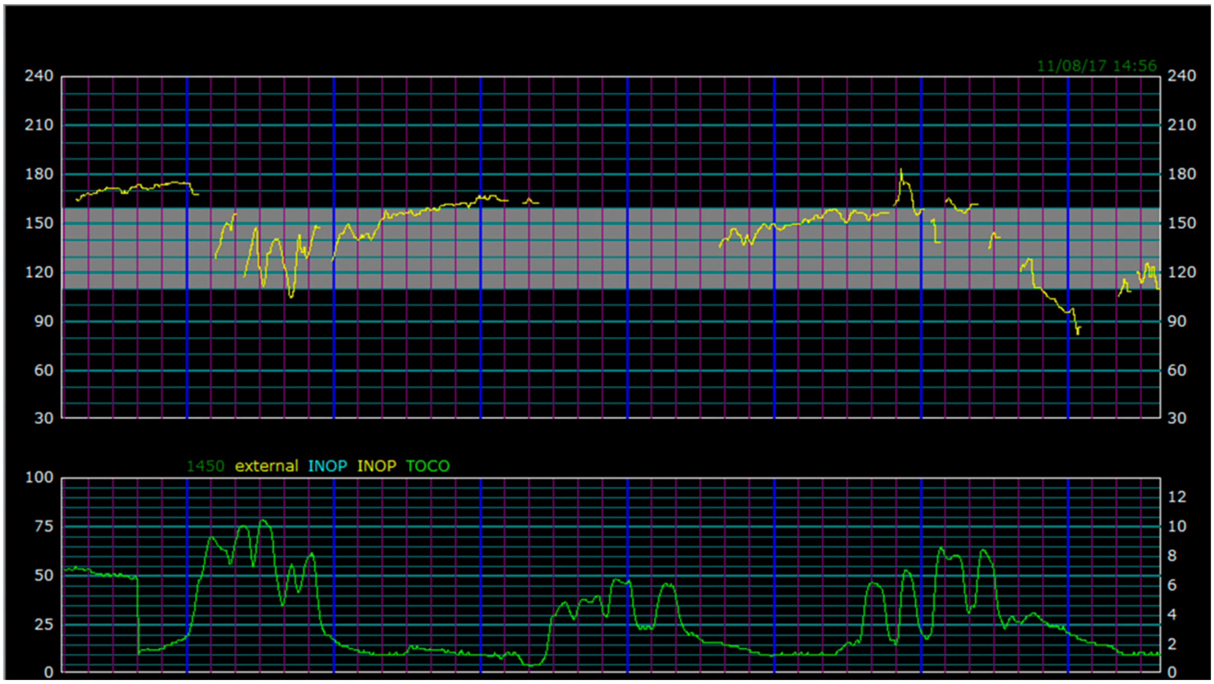

Figure 6. Electronic fetal monitoring strip 6.

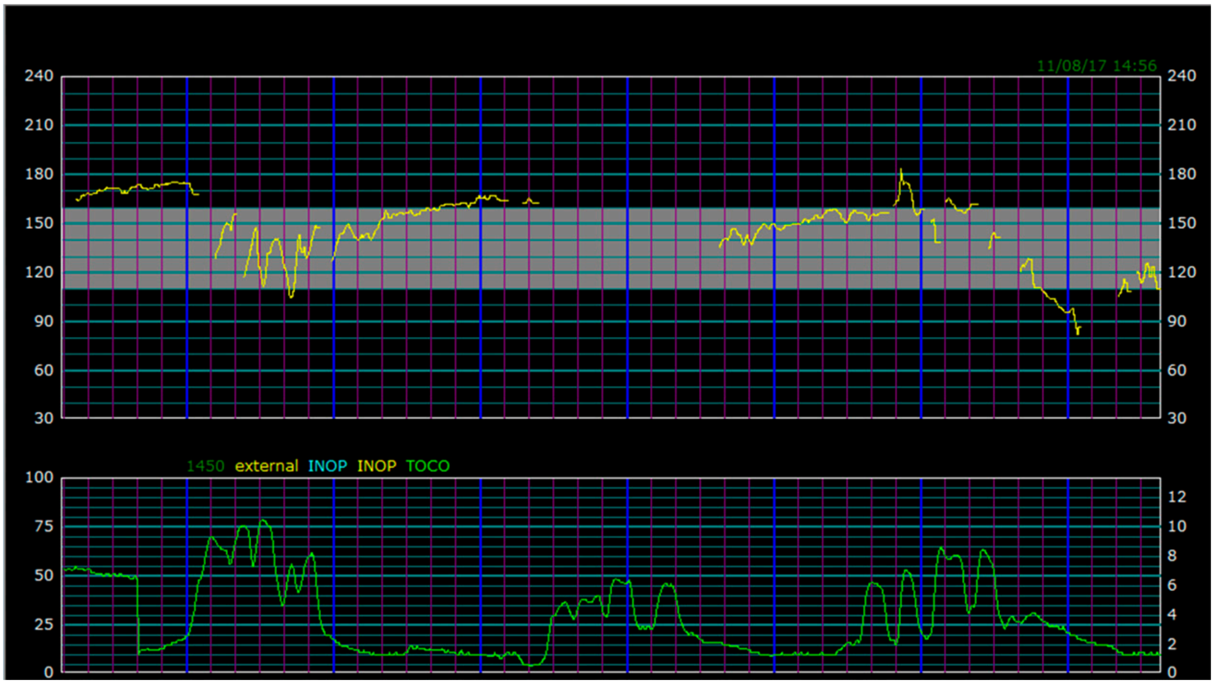

Figure 6. Electronic fetal monitoring strip 6.

Findings from EFM strip 6 are as follows:

- Baseline rate: Not established because of the absence of a continuous 2-minute segment
- Baseline variability: Not available
- Episodic patterns: None
- Periodic patterns: Variable decelerations
- Uterine contractions: Every 2 minutes "saw-tooth" contractions indicate pushing effort
- Interpretation: Category II
- Differential diagnosis: Variable decelerations
- Action: Second-stage pushing

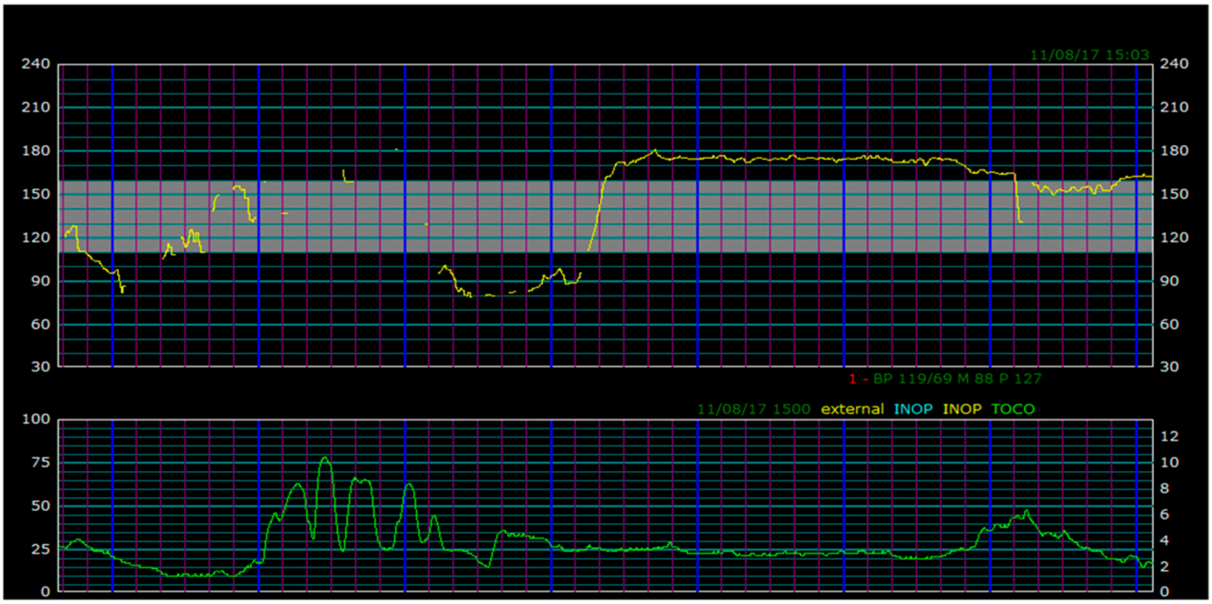

Figure 7. Electronic fetal monitoring strip 7.

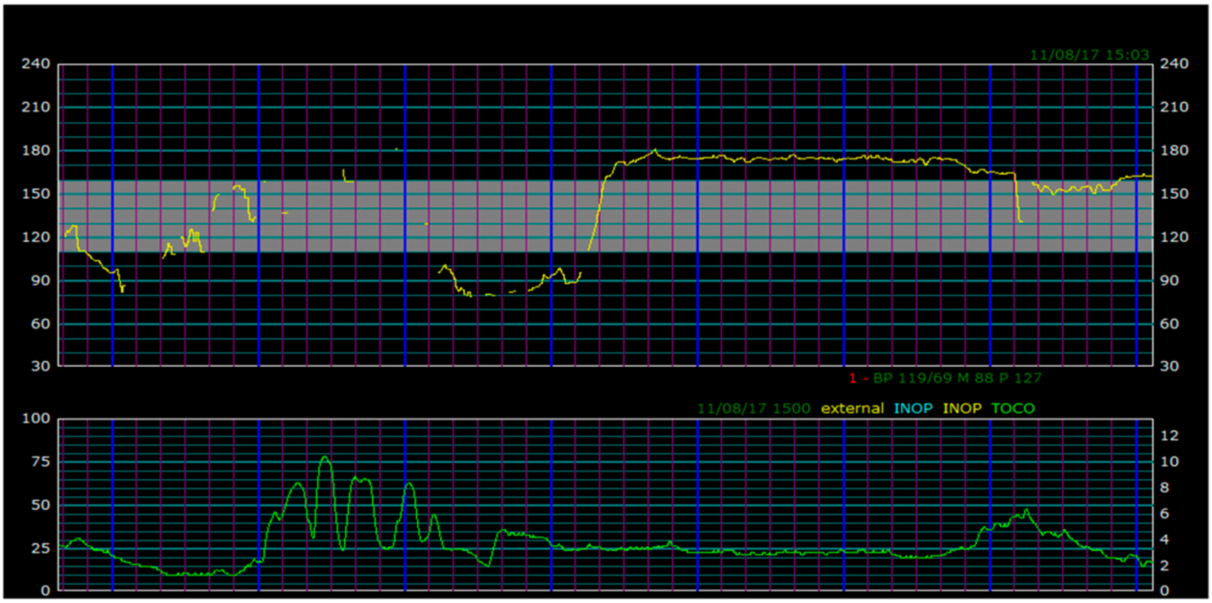

Figure 7. Electronic fetal monitoring strip 7.

Findings from EFM strip 7 are as follows:

- Baseline rate: 175 beats/min
- Baseline variability: Minimal variability
- Episodic patterns: None
- Periodic patterns: Variable decelerations
- Uterine contractions: 5 minutes "saw-tooth" contractions indicate pushing effort
- Interpretation: Category II
- Differential diagnosis: Variable decelerations
- Action: Operative vaginal delivery

A viable female infant was delivered and evaluated by the pediatricians who attended the delivery. The infant emerged vigorous and crying. The 1- and 5-minute Apgar scores were 8 and 9, respectively. The umbilical cord gases are shown in Table 2. The newborn stayed with the mother for skin-to-skin contact and roomed-in with her mother until discharge.

DISCUSSION

The intrapartum FHR tracing is interpreted within the context of the clinical history. A main factor in fetal circulation is the integrity of the placental unit to support fetal oxygenation throughout the stress of labor. The FHR tracing generated by a well-oxygenated central nervous system of the fetus will show variability. In addition, it is unlikely that normal labor will progress to the endpoint of vaginal delivery without any variable decelerations or periods of minimal variability because labor is an inherently stressful process for the fetus. Compression of the umbilical cord is likely to cause decelerations in the FHR pattern. As such, most intrapartum FHR tracings are labeled as category II, and are indeterminate in predicting fetal outcome.

TABLE 2. **Umbilical Cord Gas Measurement**

	pH	Pco$_2$ (mm Hg)	Po$_2$ (mm Hg)	Base Excess
Arterial	7.16	63.9	28	–5.6
Venous	7.32	38.3	27.8	–5.5

Several clinical factors will influence the FHR tracing, and can make interpretation of the fetal status rather challenging. This case illustrates the FHR tracing of a TOLAC. The main risk for women undergoing TOLAC is uterine rupture, which occurs in less than 1% of cases of labor after a cesarean birth. (1) Although a rare event, uterine rupture can be catastrophic for both the fetus and the pregnant woman. Uterine rupture results in interruption of blood flow to the placenta and therefore, oxygen delivery to the fetus. The fetus may be ejected out of the uterus and into the abdominal cavity. Maternal hemorrhage can lead to hypovolemic shock, further compromising blood flow to the placenta. In cases of uterine rupture, emergency cesarean delivery is often required. Physicians caring for women undergoing a TOLAC are on high alert when FHR tracing abnormalities are observed. A common sign of symptomatic uterine rupture is an abnormality of the FHR tracing. However, the specific tracing abnormality that indicates a uterine rupture is not well-established. One case-control study, in which "cases" were women with proven symptomatic uterine rupture and controls were those with successful vaginal births after cesarean, demonstrated that fetal bradycardia was the only significant difference in the FHR tracing patterns between cases and controls. (2) Women with a uterine rupture had significantly more fetal bradycardia tracing patterns. They summarized the frequency of tracing patterns associated with uterine rupture that were reported in the medical literature. The most common pattern is fetal bradycardia (33%–70% of cases), late decelerations (19%–87% of cases), and variable decelerations (5.1%–19% of cases). (2) This patient undergoing TOLAC had various abnormal FHR patterns, but the most common recurring abnormal FHR pattern was recurrent variable decelerations, which was present in both the first and second stages of the labor.

Management of recurrent variable decelerations is directed at relieving umbilical cord compression, which is likely the most common cause of this heart rate pattern. Mainstay of treatment includes maternal position change and amnioinfusion. Amnioinfusion is achieved via transvaginal placement of an intrauterine pressure catheter, through which warm normal saline is infused into the amniotic cavity. This intervention has been shown to alleviate variable decelerations, and decrease cesarean delivery rate for suspected fetal distress. (3) A scarred uterus, as is present with TOLAC, is not a contraindication to amnioinfusion. One systematic review on this subject concluded that amnioinfusion for women undergoing TOLAC was not associated with increased uterine rupture rates. (4) This review relied heavily on a 1996 study of 1,436 patients undergoing TOLAC. (5) In this older study, uterine rupture occurred in 1 in 122 (0.8%) patients who had an amnioinfusion compared with 15 in 1,314 (1.1%) who did not have an amnioinfusion. There was no significant difference in uterine rupture rate for this intervention. A power analysis for a prospective trial was presented by the authors, which showed that more than 16,000 patients would be required to show a significant difference in rupture rates, and such a study would take 10 to 20 years to complete. The poor feasibility of such a study is likely why prospective data do not exist.

Differentiating FHR abnormalities during TOLAC from those associated with uterine rupture requires consideration of all clinical signs in addition to the FHR tracing. Clinical signs and symptoms of uterine rupture include not only changes in the FHR tracing, but also significant abdominal pain, sometimes difficult to appreciate with the use of epidural anesthesia, and the loss of fetal station. The loss of fetal station may imply extrusion of the fetus into the maternal abdominal cavity. Repeat vaginal examinations in this case of TOLAC provided reassurance that the fetus continued to descend into the maternal pelvis as the station progressed from a −3 to +2 station. Clinicians who are faced with complicated tracing patterns in a high-risk labor situation must find ways to ensure a normal fetal oxygenation status. In this case, the concerning FHR patterns were alternating with category I patterns, or reassuring category II patterns. Regardless of category, the presence of moderate variability and/or accelerations is a reassuring sign because it indicates adequate autonomic output from the fetal central nervous system, and therefore adequate oxygenation. (6) Their presence is highly predictive of a normal fetal acid-base status. (3)

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the indications for and perinatal complications of operative vaginal delivery (forceps, vacuum extraction, etc) and of vaginal delivery after cesarean delivery.

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NeoReviews 2018;19;e426
DOI: 10.1542/neo.19-7-e426

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A Newborn with an Abdominal Mass

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*Washington University in St. Louis School of Medicine and St. Louis Children's Hospital, St Louis, MO

THE CASE

A newborn presents with a large left-sided abdominal mass. Transillumination can be seen on the left (Fig 1) but not the right (Fig 2).

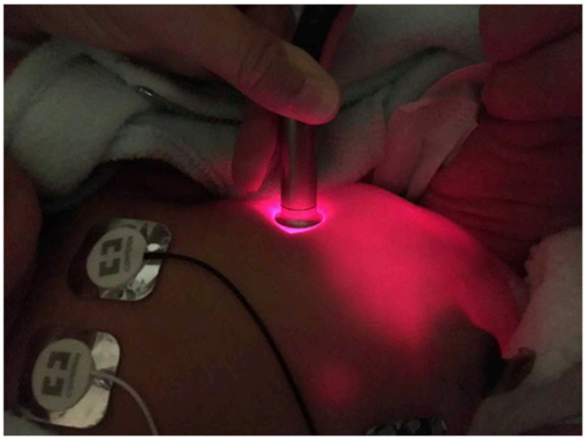


Figure 1. Transillumination of the left side of the abdomen.

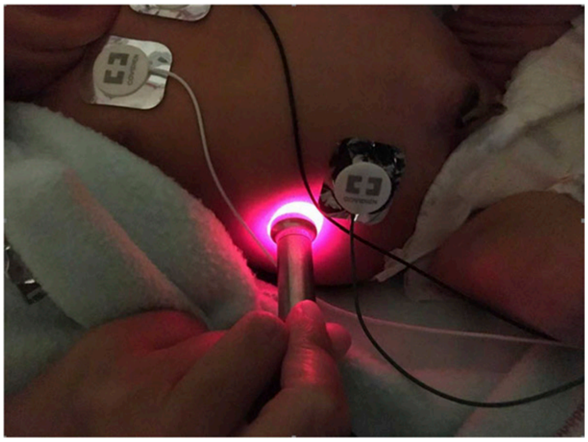


Figure 2. Right side of the abdomen with no transillumination.

Prenatal and Birth Histories

- Mother 19-year-old gravida 1 who presented to the emergency department with cervical dilation and in labor. She received no prenatal care.
- Estimated gestational age 37 to 38 weeks based on ultrasonography performed immediately before delivery.
- Infant was born via vaginal delivery in vertex position.

AUTHOR DISCLOSURE Drs Mammel and Vachharajani have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

- Maternal serologies: Blood type O positive, Coombs negative; rubella immune; group B *Streptococcus* status–unknown; hepatitis B surface antigen–negative; human immunodeficiency virus–negative; syphilis treponemal screening test–negative.
- Apgar scores 8 and 9 at 1 and 5 minutes, respectively.
- Infant cried immediately after birth. Nasal flaring noted and continuous positive airway pressure (CPAP) applied.

Presentation

Ultrasonography performed before delivery revealed findings concerning for bladder outlet obstruction. Abdominal distention was noted immediately after birth. The infant was transported to the NICU for further evaluation after bladder catheterization resulted in 2 to 3 mL of urine.

Progression (Day 1)

- Birthweight 3,260 g (80th percentile); length 49.4 cm (76th percentile); head circumference 31.5 cm (15th percentile)
- Heart rate 160 beats/min
- Respiratory rate 43 breaths/min
- Temperature 36.3°C
- Blood pressure 69/46 mm Hg

Physical Examination

- General: Female infant in open warmer receiving CPAP. Large distended abdomen.
- Skin: Warm and dry without lesions.
- Head, ears, eyes, nose, and throat examination: Molding. Anterior/posterior fontanels were soft and flat with aligned sutures; pupils equal, round, and reactive to light; ears in the normal position; no preauricular pits or tags; nares patent; mucous membranes pink and moist; palate intact; neck supple, with no masses.
- Chest: Bilateral breath sounds equal and clear with good air exchange. Symmetric chest wall movement.
- Cardiovascular: Regular rate and rhythm, no murmurs; brachial and femoral pulses 2+ and symmetric; capillary refill 2 to 3 seconds.
- Abdomen: Distended with bulging flanks bilaterally. No anterior abdominal wall erythema. No prominent veins. No visible peristalsis. Soft on palpation. Lump felt in the left hypochondrium and lumbar region. Hand could be inserted between the left costal margin and the lump. Positive transillumination of the abdomen in left hypochondrium, suprapubic, and lumbar region. No transillumination on the corresponding areas of the right side or in the suprapubic region. Dull note on percussion in the area transilluminated but tympanic note on the rest of the abdomen. Bowel sounds present. Unable to palpate liver or kidneys.
- Genitalia: Normal term female genitalia for gestational age. Anus appears patent.
- Musculoskeletal: Spine midline and intact. No sacral dimple. Hips stable bilaterally.
- Neurologic: Quiet, responsive, and reactive. Normal grasp, suck, and Moro reflexes. Tone appropriate for gestational age.

Radiographic Studies

Radiography of the chest and abdomen was performed and result is shown in Fig 3.

Abdominal ultrasonography was performed and sonographic images of the left kidney are shown in Fig 4.

Differential Diagnosis

Left-sided cystic flank mass in a newborn infant

- Hydronephrosis
- Ureteropelvic junction obstruction
- Vesicoureteral reflux
- Megaureter

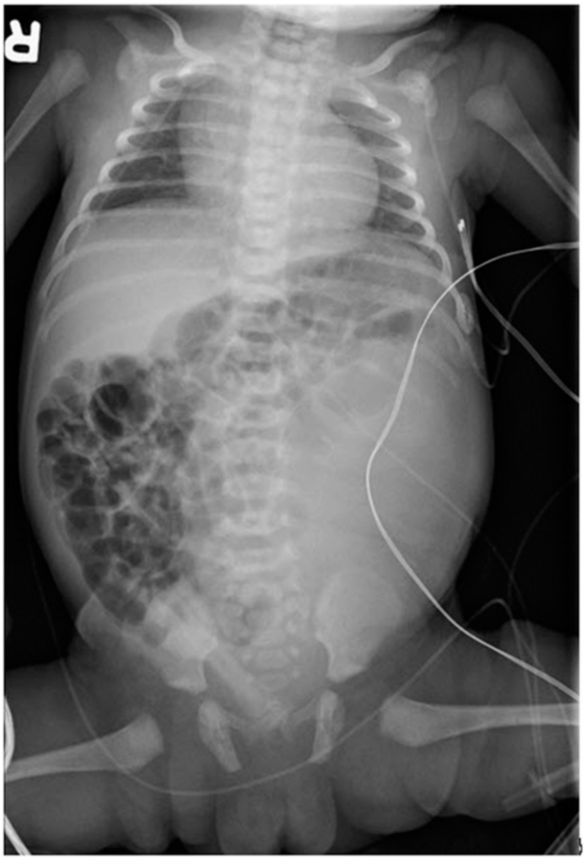


Figure 3. Radiograph of the chest and abdomen.

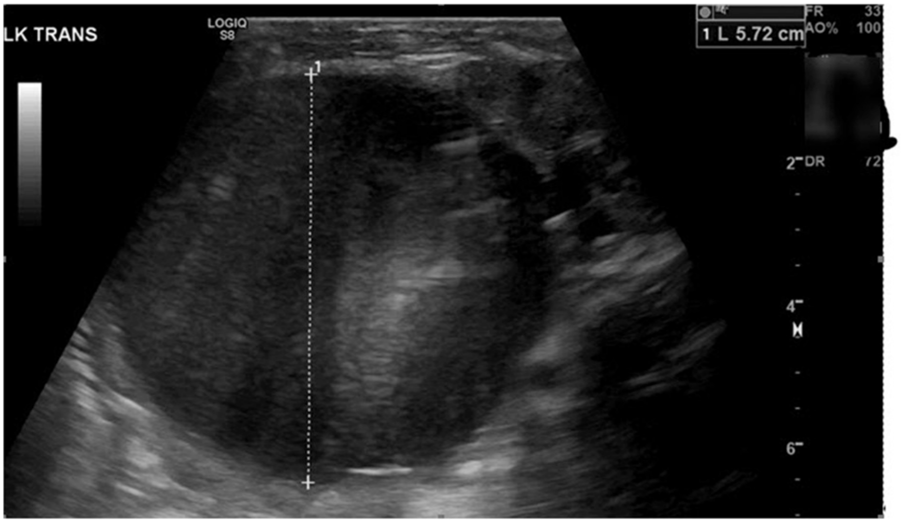


Figure 4. Abdominal ultrasound scan, transverse view of the left renal pelvis.

- Ureterocele
- Multicystic dysplastic kidney
- Autosomal recessive polycystic kidney disease

ACTUAL DIAGNOSIS

Left ureteropelvic junction obstruction

The minimal volume of urine after bladder catheterization in the delivery room made bladder outlet obstruction unlikely. The location of the unilateral lump and the ability to pass fingers between the lump and the rib cage made this unlikely to be a splenic mass and more likely to be a renal mass. The transillumination shown (Figs 1 and 2) made it very likely to be a large cystic renal mass. Because hydronephrosis caused by ureteropelvic junction (UPJ) obstruction is the most common cause of renal mass in a neonate, it was on the top of the differential diagnosis. Abdominal radiography (performed after the clinical diagnosis was made) revealed a large mass occupying the left hemi-abdomen displacing multiple nondilated loops of bowel to the right. These findings made intestinal duplication cyst or some bowel abnormality (such as meconium ileus causing abdominal distention) unlikely.

Ultrasonography revealed a large left kidney (6.9 cm) with marked dilation of the renal pelvis (Fig 4) and no ureteral dilation. The bladder was unremarkable. The right kidney was normal in size and architecture. There was no splenomegaly. These findings are consistent with left-sided UPJ obstruction.

This case highlights the value of a comprehensive physical examination—including transillumination—in narrowing the differential diagnosis; the examiner was able to determine that this was a unilateral cystic renal mass, most likely UPJ obstruction, before any imaging studies were performed.

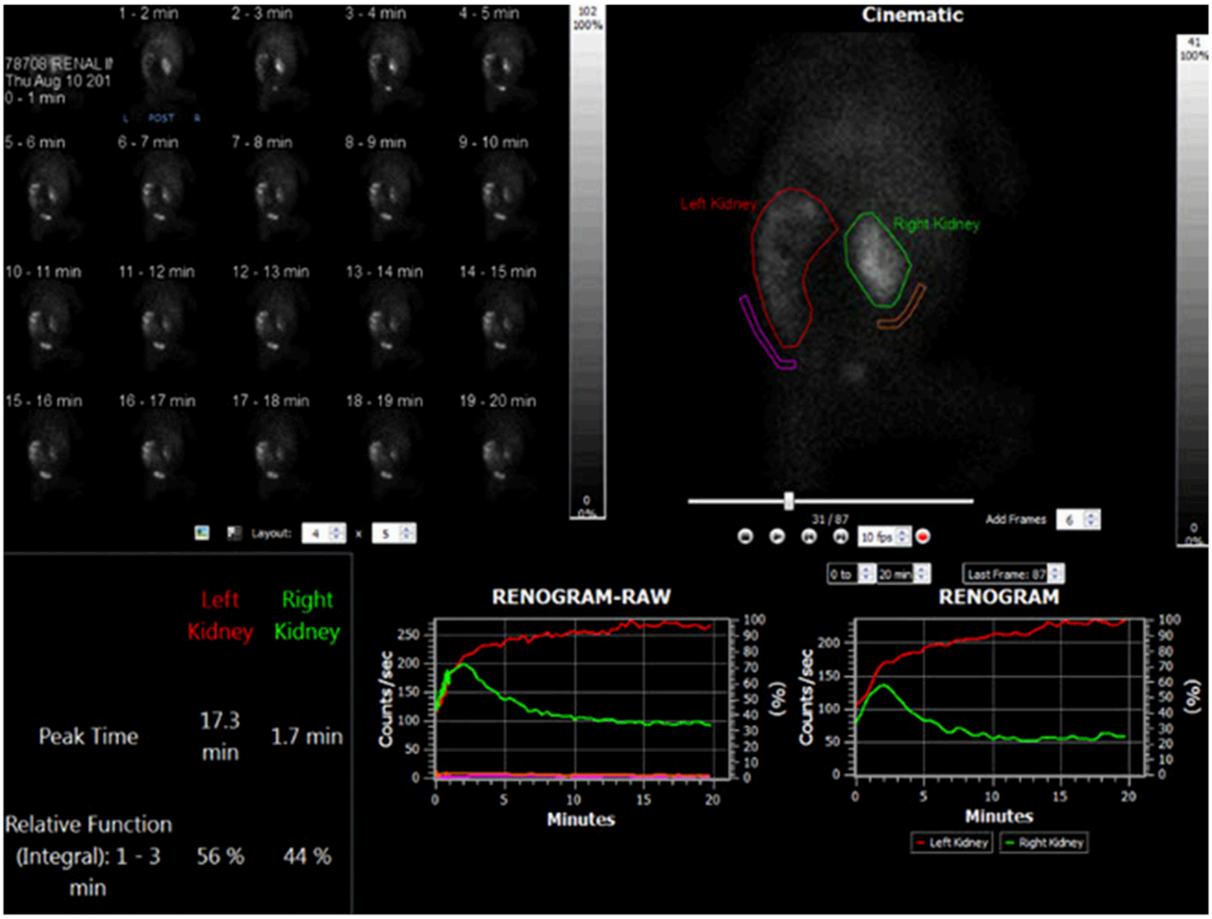
MANAGEMENT

Based on the ultrasound findings immediately before delivery, urology was consulted after admission to the NICU. Catheterization after birth returned 2 to 3 mL of urine. Ultrasonography revealed the findings described earlier, and the diagnosis of UPJ obstruction was made. Daily amoxicillin for urinary tract infection (UTI) prophylaxis was commenced, as per urology recommendation.

Radionuclide renal scanning was performed at 4 weeks of age (Fig 5), which revealed decreased blood flow to the left kidney and left hydronephrosis. There was delayed uptake and excretion with no washout of the radionuclide from the left kidney. Furosemide was administered to evaluate for obstruction. Sequential images after furosemide injection revealed no clearance of left pelvicalyceal activity. The estimated contribution of the left kidney to total renal function was 56% and that of the right kidney was 44%. These findings are consistent with normal function but obvious left UPJ obstruction.

The infant was seen by urologic surgery in follow-up clinic shortly after her radionuclide renal scan. She was doing well, continued to receive amoxicillin prophylaxis, and had been gaining weight appropriately. Because her renal function was preserved, surgery was not indicated at this time and follow-up was arranged for 3 months of age.

At the 3-month follow-up, ultrasonography showed persistent pronounced dilation of the left renal collecting



	Left Kidney	Right Kidney
Peak Time	17.3 min	1.7 min
Relative Function (Integral): 1 - 3 min	56 %	44 %

Figure 5. Radionuclide renal scan, dynamic renal study phase.

system with associated cortical thinning (Fig 6). The degree of dilation was largely unchanged from her previous visit. The urologist noted that it is likely the patient will require surgery at some point to relieve her obstruction. The dilation remained mostly extrarenal, so her renal function was expected to be preserved. She will continue to receive antibiotic prophylaxis, and ultrasonography was scheduled for 6 months of age.

WHAT THE EXPERTS SAY

UPJ obstruction is the most common cause of pediatric hydronephrosis, with an incidence of 1 in 1,000 to 1,500 newborns. (1) It is usually unilateral, and is more common in boys than in girls. (2) Congenital UPJ obstruction can be associated with other congenital renal anomalies, such as renal dysplasia, horseshoe kidney, duplicated renal collecting system, and ectopic kidney. Management can include observation, medical prophylaxis, and pyeloplasty, depending on the degree of obstruction and differential renal function.

Antenatal ultrasonography has led to earlier diagnosis and management of hydronephrosis; antenatal hydronephrosis (ANH) is detected in up to 1% to 5% of infants. (3) However, the causes of ANH must be determined, because in 41% to 88% of cases, ANH is transient and resolves by birth or during infancy. (3) The most common pathologic causes of ANH are UPJ obstruction (10%–30%), vesicoureteral reflux (10%–20%), and megaureter (5%–10%). Postnatal ultrasonography is used to stratify the risk of pathologic causes for hydronephrosis and to determine the degree to which a patient is evaluated. The current recommendations involve using the renal pelvis anteroposterior diameter and/or Society for Fetal Urology (SFU) grading. The latter uses a grading scale of 0 to 4, with 0 indicating no hydronephrosis and 4 indicating a dilated renal pelvis, multiple fluid-filled calyces throughout the kidney, and thinning of the renal parenchyma over the calyces. (4)

The causes of UPJ obstruction are generally divided into intrinsic and extrinsic. The pathophysiology of intrinsic

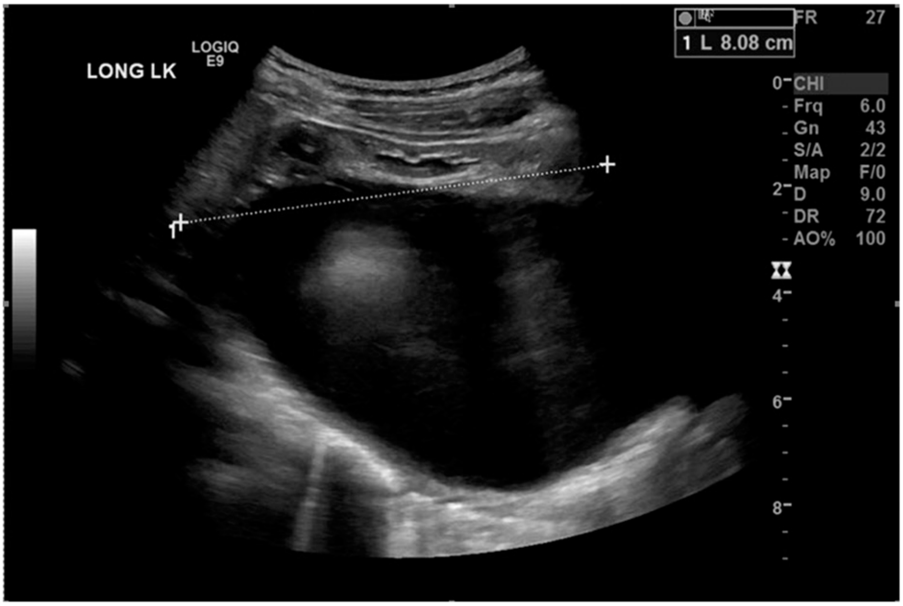


Figure 6. Renal ultrasound scan. Long view of the left renal pelvis.

obstruction is unclear, but is thought to be caused by a combination of factors, including muscular discontinuity at the site of the UPJ, improper innervation, and ureteral hypoplasia. (5) Extrinsic obstruction can be caused by compression from an overlying renal vessel. Patients with intrinsic UPJ obstruction are typically diagnosed within the first year of age, while extrinsic UPJ obstruction is typically diagnosed later in childhood. (6)

Ultrasonographic evaluation is the initial modality of choice for postnatal evaluation of suspected UPJ obstruction. The timing of ultrasonography varies based on the degree of suspected obstruction; mild to moderate hydronephrosis should be evaluated within 3 to 7 days, after the period of transient neonatal dehydration in the first 48 hours after birth. In the case of severe hydronephrosis, suspected posterior urethral valves, or oligohydramnios, ultrasonography should be performed at 24 to 48 hours. (7) Subsequent radionuclide renal scan is often used to determine renal function and degree of obstruction.

A radionuclide renal scan involves the injection of a radiolabeled tracer into the venous system and tracked with a γ camera to evaluate renal function and distinguish obstructive versus nonobstructive causes of renal or ureteral dilation. The preferred radiotracer in infants is 99mTc-mercaptoacetyltriglycine (99mTc-MAG3). As shown in Fig 5, the first phase of the study is the dynamic renal study, which evaluates renal function, size, and position. The diuretic phase, shown in Fig 7, allows evaluation for obstruction. Interpretation of the diuretic phase depends on the timing of diuretic administration. In the radionuclide renal scan shown in Fig 7, when the diuretic is injected more than or equal to 20 minutes after the radiotracer, a T1/2 less than 10 minutes usually means the absence of obstruction, and a T1/2 greater than 20 minutes usually signifies obstruction. (8)

UPJ obstruction has a broad range of effects with respect to long-term functioning of the kidney, from reversible hydronephrosis to renal failure requiring pyeloplasty or nephrectomy. (9) The management varies, depending on the degree of obstruction and renal function in the affected kidney. The goals of treatment are to prevent or minimize renal injury and optimize long-term outcomes.

The use of prophylactic antibiotics in UPJ obstruction remains controversial. The risk of UTI has been shown to be significantly increased in those with SFU grade 3 or 4 compared with grade 1 or 2. (10) Accordingly, antibiotic prophylaxis with amoxicillin is recommended in the management of severe obstruction. (11)

Conservative management with serial radionuclide renal scans/ultrasonography is appropriate for infants with unilateral UPJ obstruction and differential renal function greater than 40% on the affected side. Indications for pyeloplasty vary by institution and clinician preference, but can include:

- Differential renal function less than 40% or a decline of greater than or equal to 5% on serial radionuclide renal scans
- Bilateral severe UPJ obstruction
- Recurrent UTI while taking antibiotic prophylaxis

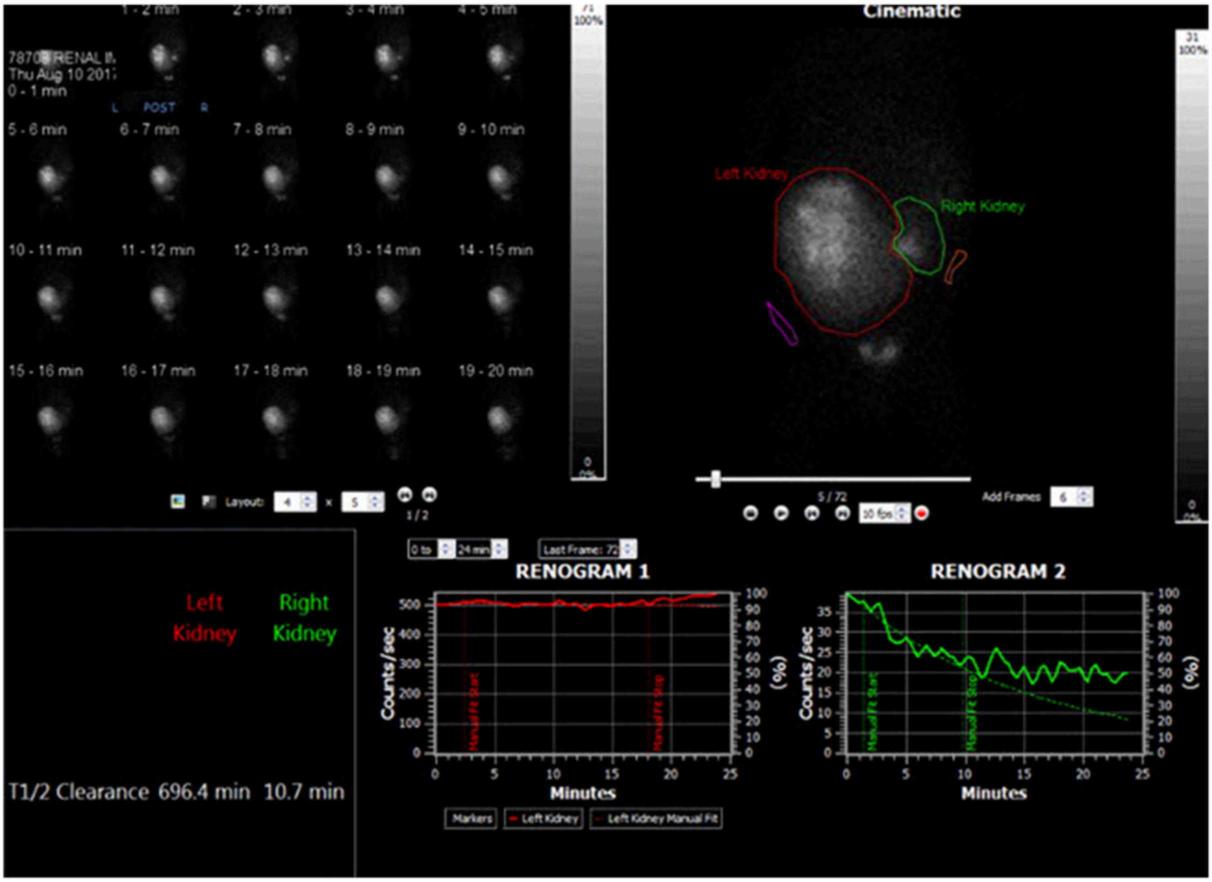


Figure 7. Radionuclide renal scan, diuretic phase. The patient was given furosemide via slow intravenous injection; sequential images obtained after diuretic administration are shown. Prompt clearance of activity from the pelvicalyceal system can be seen on the right, while the left shows no clearance of pelvicalyceal activity.

Retrospective studies have shown surgical intervention rates in patients with a conservative management profile to be as high as 55%. (12) However, a prospective randomized study performed by SFU comparing conservative and surgical management found a surgical intervention rate of 25% in the conservative management group. (13) It should be noted that in the SFU study, renal function stabilization was similar for either surgical or conservative management.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical manifestations of anatomic abnormalities of the kidneys and urinary tract in infants.
- Know how to diagnose specific anatomic abnormalities of the kidneys and urinary tract in infants.

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A Newborn with an Abdominal Mass

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Answer Key appears on page e506.

Neonatal Hypotonia

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Education Gaps

1. Clinicians should recognize that generalized hypotonia is a common clinical presentation in the neonate that may be a manifestation of systemic illness, central nervous system dysfunction, or peripheral nervous system dysfunction.
2. With the introduction of newer therapeutic modalities, some of the causes of neonatal hypotonia are now treatable. Therefore, recognizing symptoms and pursuing appropriate and timely evaluation may positively affect outcomes.
3. An understanding of the localization-based differential diagnosis is important in the approach to the evaluation of these infants.

Abstract

Neonatal hypotonia represents a commonly encountered issue in the NICU and newborn nursery. Low tone is not a diagnosis in itself but, rather, a symptom. This review focuses on the special case of diffuse hypotonia presenting in the neonatal period. Etiologies are broad and include systemic illness, dysfunction of the central nervous system, or dysfunction of the peripheral nervous system and motor unit (ranging from disorders of the anterior horn cell to primary muscle disease). In this time of rapidly expanding therapeutic options for many diagnoses causing hypotonia, expeditious evaluation is crucial. Careful physical examination, thorough history, and appropriately selected ancillary testing guides the diagnostic process.

Objectives After completing this article, readers should be able to:

1. Describe the key components of the history and physical examination relevant to the assessment of the hypotonic infant.
2. Discuss the differential diagnosis of generalized hypotonia in the neonatal period.
3. Identify major treatable causes of neonatal hypotonia that should not be missed.

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ABBREVIATIONS

CK	creatine kinase
CMS	congenital myasthenic syndrome
CMT	Charcot-Marie-Tooth neuropathy
CNS	central nervous system
EMG	electromyography
HIE	hypoxic-ischemic encephalopathy
MRI	magnetic resonance imaging
PNS	peripheral nervous system
SMA	spinal muscular atrophy
WES	whole exome sequencing

INTRODUCTION

The classic "floppy baby" represents a challenging clinical scenario for pediatricians and child neurologists alike. Although spasticity generally indicates dysfunction at the level of the brain or spinal cord, low tone in an infant is a nonspecific sign that is not localizing. Hypotonia may be a manifestation of systemic illness, central nervous system (CNS) dysfunction, or peripheral nervous system (PNS) dysfunction. Within the category of PNS dysfunction, clinicians must consider disorders of the anterior horn cell, peripheral nerve, neuromuscular junction, or muscle. Additional causes include systemic conditions such as metabolic disorders, infection, hypothyroidism, and chromosomal anomalies. The differential diagnosis evolves as the infant ages. This review focuses on the evaluation of diffuse hypotonia in the neonatal period, considering first systemic involvement, CNS dysfunction, and finally PNS dysfunction.

At first glance, a neonate with an epileptic encephalopathy may be indistinguishable from a neonate with a congenital myopathy. These 2 infants (and families), however, require different care and counseling. The clinical history and examination findings narrow the differential diagnosis and guide further evaluation. With careful assessment and use of appropriate ancillary testing, clinicians can often identify the etiology of the hypotonia. In a time of rapidly expanding treatment opportunities, accurate and timely diagnosis is crucial. This is perhaps best exemplified by the development of a new therapy for spinal muscular atrophy (SMA), a previously untreatable and life-limiting disorder in its infantile form. (1)(2) An organized, systematic approach to evaluation aids the diagnostic process. Here, we review a localization-based differential diagnosis for the diffusely floppy infant. An overview of this approach is summarized in the Fig.

OBTAINING THE HISTORY

A careful perinatal and birth history helps guide the evaluation. It is important to inquire about the frequency, as well as any changes, in fetal movements during the pregnancy. The history should also include the patient's gestational age, Apgar scores (because appropriate tone varies based on gestational age), and medications prescribed to the patient. The Apgar score and delivery history aid in determining if the hypotonia is an acute or semiacute process, and if there was any clear precipitating event. Knowledge of maternal serologic testing and infectious exposures (eg, exposure to varicella, cytomegalovirus, or Zika virus) may raise suspicion for a congenital infection. Maternal and family medical histories provide critical information that can help narrow the differential diagnoses.

PHYSICAL ASSESSMENT OF THE NEONATE

The neurologic examination of a neonate is a complex task. Observation is a key aspect of the physical examination. Although the approach to examination is the same when assessing for generalized or focal hypotonia, we will focus specifically on the diffusely floppy neonate.

The presence of dysmorphic facial features or other general examination features, including organomegaly, microcephaly, skin abnormalities, and early joint contractures or arthrogryposis, may suggest multisystem involvement. The mental status will inform the differential diagnosis and guide further evaluation. Recognition of a sleepy, encephalopathic newborn should trigger an evaluation for systemic illness such as infection, metabolic derangement, hypoxic-ischemic encephalopathy (HIE), or some other process causing diffuse CNS dysfunction. A diagnosis of HIE is more likely if the history indicates that there was an acute perinatal or intrapartum event. Because infants are more sedated after they eat, the physical examination should also mention when they were examined in relation to a feeding.

Certain physical examination features aid in the localization of muscle weakness. Evaluation of facial strength (grimace, ability to fully bury eyelashes), ability to suck and swallow, strength of cry/cough, and eye movements serve to evaluate bulbar function. Prominent abnormality in one of these functions may suggest a neuromuscular or multisystem disorder, though these abnormalities can be found in CNS dysfunctions as well.

The examiners should also observe the complexity of movements. This serves as an assessment of neurologic maturity. Normal patterns consist of a variable sequence of movements involving the arms, legs, and trunk. (3) Typical movements should be asynchronous and involve all extremities. Movements should not be asymmetric and should not occur en bloc. Signs of pathology and hypotonia would be suggested if the movements are not complex or variable in nature. The lack of movements is correlated with the degree of hypotonia.

Tone is defined as the internal state of the muscle (tone is fiber tension within individual muscles and muscle groups), or the degree of muscle tension or resistance during rest in response to stretching. Both postural (central) and peripheral tone must be assessed. It is therefore necessary to assess pronation/supination to bypass the flexor predominance in the neonatal period. It is important to observe the infant when the head is in the midline position; this prevents

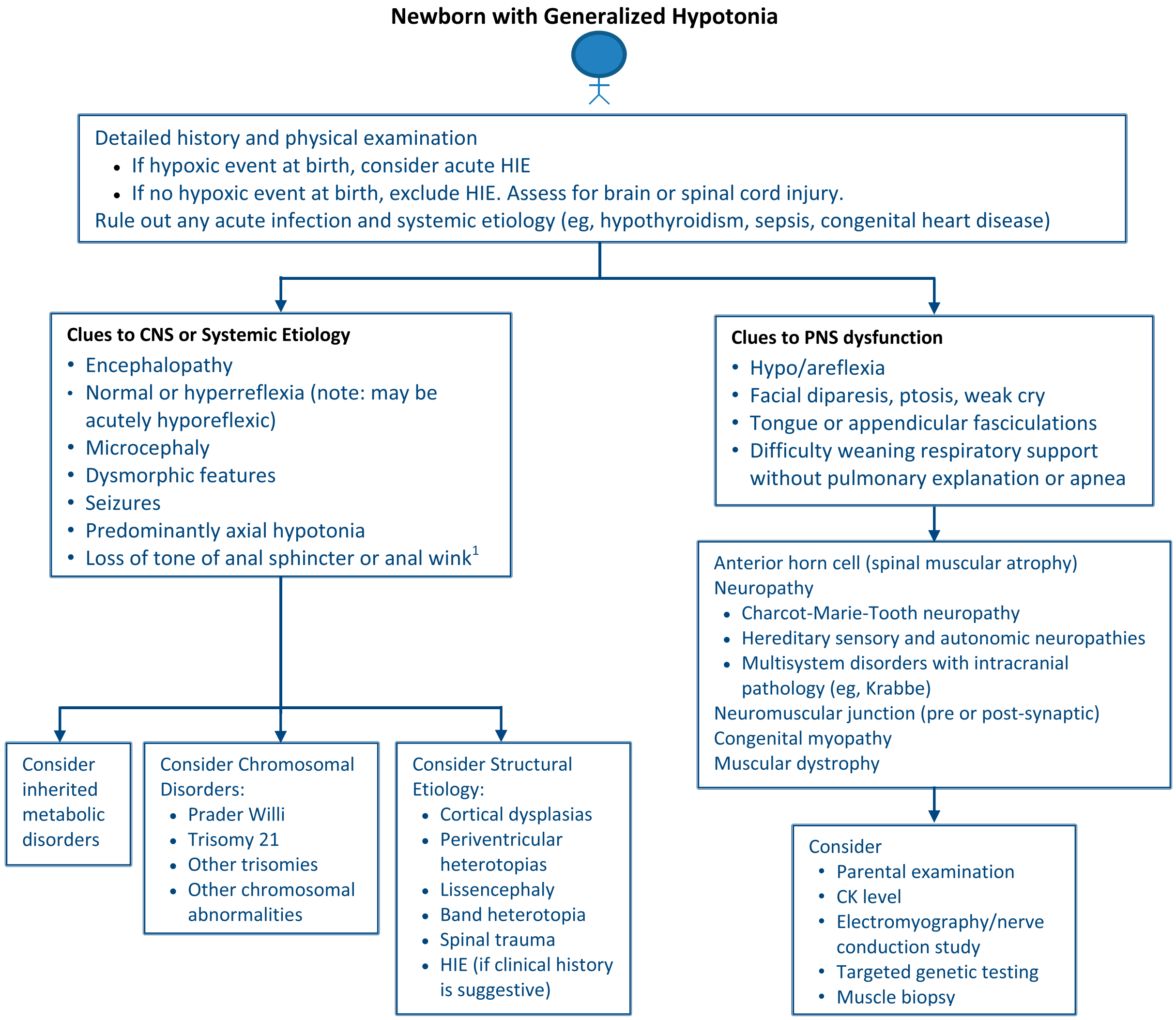
Newborn with Generalized Hypotonia
Detailed history and physical examination
If hypoxic event at birth, consider acute HIE
If no hypoxic event at birth, exclude HIE. Assess for brain or spinal cord injury.
Rule out any acute infection and systemic etiology (eg, hypothyroidism, sepsis, congenital heart disease)
Clues to CNS or Systemic Etiology
Encephalopathy
Normal or hyperreflexia (note: may be acutely hyporeflexic)
Microcephaly
Dysmorphic features
Seizures
Predominantly axial hypotonia
Loss of tone of anal sphincter or anal wink1
Clues to PNS dysfunction
Hypo/areflexia
Facial diparesis, ptosis, weak cry
Tongue or appendicular fasciculations
Difficulty weaning respiratory support without pulmonary explanation or apnea
Anterior horn cell (spinal muscular atrophy)
Neuropathy
Charcot-Marie-Tooth neuropathy
Hereditary sensory and autonomic neuropathies
Multisystem disorders with intracranial pathology (eg, Krabbe)
Neuromuscular junction (pre or post-synaptic)
Congenital myopathy
Muscular dystrophy
Consider inherited metabolic disorders
Consider Chromosomal Disorders:
Prader Willi
Trisomy 21
Other trisomies
Other chromosomal abnormalities
Consider Structural Etiology:
Cortical dysplasias
Periventricular heterotopias
Lissencephaly
Band heterotopia
Spinal trauma
HIE (if clinical history is suggestive)
Consider
Parental examination
CK level
Electromyography/nerve conduction study
Targeted genetic testing
Muscle biopsy

Figure. An approach to a neonate with generalized hypotonia. CNS=central nervous system; CK=creatine kinase; HIE=hypoxic-ischemic encephalopathy; PNS=peripheral nervous system. [1]Loss of anal sphincter tone or wink is not specific for spinal cord dysfunction and may also be abnormal in some PNS disorders such as myotonic dystrophy.

activation of the tonic neck reflex, which would cause a false asymmetry in tone. The normal resting posture of a healthy newborn is characterized by flexion in the arms and legs. The hypotonic infant may be placed with arms in extension and hips in abduction ("frog leg posture"). Manual muscle strength cannot be tested in a neonate.

Axial tone is assessed by evaluating for head lag and slip through. To assess head lag, the infant is placed supine and pulled by the arms to the sitting position. If the infant has neurologically normal examination findings, the arms will remain partially flexed at the elbows. The infant's head should lag behind the body but should not be fully flexed backward. Vertical suspension should allow for the infant to be held by the examiner under the arms and around the chest without the infant "slipping through" his/her hands. Premature neonates are expected to have lower tone than gestationally mature counterparts, such that gestational age must be taken into account when judging tone.

Assessing motor function of the arms and legs begins with passive range of motion in the full-term infant. The examiner should rotate each joint to feel the resistance and the range of motion. Assessment of arm supination and pronation allows for evaluation without misinterpretation of the normally predominant flexor tone seen in newborns. Arm recoil is tested by holding the arms in flexion for a few seconds then quickly extending and releasing the arm. The arm should return to the original flexed position. Similarly, assessment of leg recoil starts with flexion of the legs onto the abdomen for a few seconds. One can also measure the popliteal angle (the angle between the thigh and the leg), which is typically 90 degrees. A wider angle suggests hypotonia.

Tone of the shoulder girdle is evaluated by moving the infant's hand to the opposite shoulder. In a neurologically appropriate infant, the infant's hand does not pass the shoulder and the infant's elbow cannot cross the midline of the chest. The "scarf sign" is defined by the hand reaching past the shoulder, an indication of hypotonia in a full-term infant. (4)

The reflexes being normal, increased, or absent can help distinguish between an upper motor versus a lower motor neuron lesion. Reflexes should be tested after the assessment in tone to avoid upsetting the infant and falsely increasing the tone. Hyperreflexia may be characterized by pathologic spread of reflexes (eg, finger flexion on testing of the brachioradialis reflex) or sustained clonus. This suggests upper motor neuron dysfunction related to a process affecting the brain or spinal cord. Asymmetry of reflexes indicates a focal process. Asymmetric hyperreflexia may indicate a focal lesion of the CNS, whereas asymmetric hyporeflexia may reflect injury of a nerve root or plexus.

In addition to the deep tendon reflexes, newborn reflexes should be tested. These include the Moro reflex, tonic neck reflex, and withdrawal reflex. It is helpful to recognize the infant's gestational age to determine which reflexes are expected to be present. The palmar grasp and Moro reflex first appear at 28 weeks' gestation, though they are weak. The asymmetric tonic neck reflex, stepping reflex, and a stronger sucking reflex emerge at 34 weeks' gestation. The healthy term infant has a strong grasp, full Moro reflex, and placing reflex.

By identifying signs and patterns that accompany hypotonia, a tailored differential diagnosis can be developed.

LOCALIZATION-BASED ASSESSMENT OF HYPOTONIA

Multisystem and Systemic Disorders

Hypotonia does not imply a purely neurologic disorder. The triad of areflexia, hypotonia, and weakness in a neonate is not specific to a single class of disease and can localize throughout the motor unit. Abnormally low tone and weakness can be a manifestation of systemic illness or a chromosomal anomaly. Change in tone may be a heralding sign of sepsis in a neonate. Exposure to drugs/medications should also be considered. For example, an infant born to a mother treated with magnesium sulfate for preeclampsia may display hypotonia at birth that improves over time. Profound hypotonia in an infant without other signs of systemic illness should prompt consideration of Prader Willi syndrome. (5) Inborn errors of metabolism deserve consideration as well. The early infantile form of Pompe disease (acid maltase deficiency, glycogen storage disease type 2) represents a now treatable disorder. Severely affected infants can present in the neonatal period with hypotonia, cardiomyopathy, and hepatomegaly. Treatment with enzyme replacement improves ventilator-free survival and leads to improvements in cardiac function, though there have been no randomized controlled trials with placebo to firmly establish long-term benefits. (6) In addition to Pompe disease, other metabolic disorders that present in the neonatal period include peroxisomal disorders (Zellweger syndrome), mitochondrial cytopathies, and disorders of creatine metabolism. Organic acidurias, amino acidopathies, fatty acid oxidation disorders, and urea cycle defects may present early as well. Infants with inherited metabolic disorders are often medically sick, and laboratory abnormalities can help further direct the evaluation. Although statewide newborn screening can help identify many of the treatable inherited metabolic disorders, panels vary among states and the results are not immediately available. Clinical concern for a metabolic disorder warrants immediate evaluation in the NICU.

Central Nervous System

Brain. Clinical signs to suggest central hypotonia include encephalopathy, seizures, dysmorphic features, multiorgan abnormalities, hyperreflexia, or known genetic/chromosomal abnormalities. A careful history may also aid in the diagnosis. Pregnancy history should assess for complications including decreased fetal movements, polyhydramnios, maternal exposures (drugs and infections), and gestational age. The delivery history must include type of delivery, Apgar scores, and need for resuscitation. Evidence of hypoxia and low Apgar scores are suggestive of HIE.

Several entities are associated with an acute injury that can have hypotonia as a prominent feature, such as HIE. HIE is a clinical syndrome that evolves after an acute peripartum or intrapartum event, resulting in disruption of the fetoplacental circulation and subsequent decreased brain perfusion. Clinical findings include cardiorespiratory failure, altered sensorium, hypotonia, poor feeding, and/or seizures. (7) This is one of the first diagnoses to consider when there is a history of hypoxia, acidemia, and low Apgar scores. We often characterize this as a brain disease, but it is a multisystem effect of global hypoxia that results in hypotonia. Physical examination, blood gas, and head ultrasonography may be used to assess the severity of the cerebral edema. In the first 10 days after birth, several distinct imaging patterns of brain injury have been identified in affected infants. Typical patterns of injury involve motor tracts and may have long-term sequelae on muscle tone. Such areas affected include the deep gray matter (basal ganglia and thalamus), hippocampus, brainstem, watershed areas, and mixed patterns. (8)(9) At birth, the infant is typically floppy and encephalopathic. Clinically, loss of muscle tone is an immediate response to severe brain injury. Depending on the site, extent of injury, and age of the infant, increased tone appears as hemiplegia or quadriplegia in the term infant and diplegia in the preterm infant. These deficits are typically permanent and nonprogressive. Therapeutic hypothermia is now the standard of care for term and near-term infants with moderate to severe HIE.

Intracerebral and intraventricular hemorrhage may also affect the infant's muscle tone depending on the severity/extent of the bleeding. Intraventricular hemorrhage with periventricular leukomalacia can be seen in premature infants. Such injury can be associated with motor and cognitive deficits depending on the location and extent of the injury.

Cerebrovascular accidents (ischemic or hemorrhagic) can occur perinatally and lead to focal brain lesions that can cause asymmetry/abnormality on an infant's motor examination. The infant may present with generalized hypotonia or focal weakness depending on the size and location of the lesion. Such an infant may demonstrate an asymmetry in tone that can ultimately result in lateralized signs of upper motor dysfunction, such as hemiparesis, over time. Alternatively, these infants may remain asymptomatic during the first few months of age. Development of early hand preference during the first year after birth, seizures, or both, may be the first sign of their impairment.

Other conditions that can present with hypotonia (often without evidence of an acute injury) include malformations in cortical development. These are often caused by disruption of neuronal proliferation, neuroblast migration, and neuronal organization. Resulting abnormalities include microcephaly, megalencephaly, cortical dysplasia, periventricular heterotopia, lissencephaly, or band heterotopia that can be seen on magnetic resonance imaging (MRI) of the brain. (8) Clinically, these patients present with hypotonia and difficulty feeding. Genetic testing should be performed to aid in prognosis and family planning.

Spine. Spinal cord dysfunction should be suspected in severely hypotonic infants with paraplegia with hyper- or hyporeflexia and bowel/bladder dysfunction (abnormalities in rectal tone). Spinal cord trauma caused by a contusion or transection of the cord is rare in infants but can lead to severe sequelae. Other causes include a spinal cord tumor, paraspinal infection, syrinx, or spinal dysraphism including a myelomeningocele of the distal spinal cord and spinal column. Lesions in the cervical area may present with generalized hypotonia early in life. The most common site of myelomeningocele is the lumbosacral region and is associated with segmental hypotonia. The lumbosacral meningomyelocele affects bladder and bowel function with partial or complete paralysis of the legs. Infants who have a sacral dimple larger than 5 mm in diameter, located more than 2.5 cm above the anal verge, or associated with cutaneous findings, should undergo further evaluation. Myelomeningocele repair is traditionally performed within 72 hours of birth to minimize the risk of meningitis.

Disorders of the Motor Unit: From Anterior Horn Cell to Muscle Fiber

Disorder of the Anterior Horn Cell. A previously untreatable neurodegenerative disorder, SMA deserves special attention. In its classic form, SMA is an autosomal recessive disorder caused by loss (or less commonly mutation) of both copies of the *SMN1* gene. Severity of the clinical presentation is determined by the copy number of *SMN2*, a rescue protein; patients with fewer copies of *SMN2* display a more severe phenotype.

Infantile-onset SMA (type 1 SMA, Werdnig-Hoffman disease) may present in the early neonatal period with hypotonia, areflexia, poor suck/feeding, or respiratory weakness. Arthrogryposis should also prompt consideration of this diagnosis. Mental status is unaffected unless a secondary issue is at play, such as hypercarbia in the setting of respiratory failure. Examination reveals hypotonia, weakness, and areflexia. Fasciculations of the tongue may or may not be present initially. Bulbar dysfunction may be prominent. Respiratory weakness may manifest as tachypnea, increased work of breathing, or even paradoxical breathing. (10) It should also be noted that infants often present beyond the neonatal period, after an initial honeymoon phase in the first weeks to months of age; a neonate born to 2 parents known to be carriers of SMA should still be tested after birth even if examination findings are normal. In fact, SMA can present throughout the lifespan.

With the advent of treatment for SMA, this has become a "do not miss" diagnosis. Nusinersen, an antisense oligonucleotide, became available in late 2016. This intrathecal therapy allows for production of more full-length SMN protein by altering transcription of the *SMN2* gene. (11)(12) Treated infants have been found to have clinically significant improvement in motor milestones and in ventilator-free survival. Clinical trials are also under way for single-dose gene therapy using an adeno-associated viral vector; phase I studies are encouraging. (13) Currently, a phase III trial is under way and actively enrolling patients.

Without treatment, type 1 SMA leads to loss of motor milestones and either death or need for mechanical ventilation by 2 years of age. With newer therapies, the clinical course of this disease is now forever changed. Rapid diagnosis and initiation of treatment is crucial to improve outcomes, such that diagnosis of SMA in a newborn should be considered a neuromuscular emergency. Genetic testing is readily available and can be quickly performed so as to expedite initiation of treatment.

Disorders of Peripheral Nerve including Congenital Hypomyelinating Neuropathy and Hereditary Sensory and Autonomic Neuropathies. Hereditary neuropathies can present in the neonatal period. The classic example of this is a congenital hypomyelinating neuropathy and the more commonly known Dejerine-Sottas disease, both considered subtypes of Charcot-Marie-Tooth neuropathy (CMT). Although many genes have been implicated in the various forms of hereditary neuropathy, *PMP22*, *MPZ*, and *ERG2* are the most commonly involved causative genes in the neonatal forms of CMT neuropathy. (14). Although CMT can be inherited in an autosomal dominant or recessive manner, mutations are also often spontaneous in infantile-onset cases. In addition to hypotonia and weakness, bulbar dysfunction and respiratory weakness may be prominent. Early contractures or even arthrogryposis may be seen. (14)(15) A hypotonic, areflexic neonate with prominent dysautonomia should prompt consideration of a hereditary sensory and autonomic neuropathy (including the Riley-Day syndrome). (14)(15) Electrodiagnostics may be of use when considering the rare possibility of a hereditary neuropathy presenting very early in life.

Neuromuscular Junction. Dysfunction of neuromuscular transmission can present in the neonatal period and includes transient neonatal myasthenia, the rare congenital myasthenic syndromes, and botulism. Neuromuscular junction disorders can result from pathology at the presynaptic, synaptic, or postsynaptic level. Regardless of etiology or localization within the junction, infants with these disorders can present with hypotonia, poor feeding, ptosis, and respiratory weakness.

Transient neonatal myasthenia refers to the passively acquired, self-resolving disorder of infants born to mothers affected by autoimmune myasthenia gravis. Transplacentally acquired antibodies cause postsynaptic impairment of neuromuscular transmission. Symptoms include ptosis, hypotonia, weak cry, bulbar weakness, and respiratory difficulty or failure. (16) Affected infants generally present within the first 2 days after birth, though longer times to onset have been reported. (17)

It should be noted that transient neonatal myasthenia has been diagnosed in infants born to mothers without preexisting myasthenia diagnosis, because myasthenia gravis is an underrecognized disorder. Because the examination findings in the infant may be nonspecific, examination of the mother may be useful; fluctuating, alternating ptosis, facial weakness, or fatigable extremity weakness may point toward this diagnosis. Treatment of the infant with acetylcholinesterase inhibitors (pyridostigmine), respiratory support, and feeding support may be necessary until symptoms begin to improve. Transient neonatal myasthenia has even been reported in mothers with seronegative myasthenia gravis. (17) Rare cases of arthrogryposis have also been described in infants born to women with myasthenia. (18)

Congenital myasthenic syndrome (CMS) represents a separate entity. (19) This group of disorders represents inherited/genetic defects of neuromuscular transmission caused by a mutation in genes responsible for the neuromuscular junction (presynaptic, postsynaptic, or synaptic). Multiple genes have been implicated in CMS. Children affected by CMS can present in childhood or as early as the newborn period. Features such as (fluctuating) ptosis, bulbar dysfunction, and weakness can make this class of disorder challenging to differentiate from other neuromuscular causes of hypotonia. Repetitive nerve stimulation can be useful but is nonspecific, and may be abnormal in other conditions such as mitochondrial disorders. Electromyography (EMG) may be misleading, because EMG findings can appear myopathic in some cases. Careful clinical assessment paired with electrodiagnostics and genetic evaluation can help make this diagnosis. (19)(20) Like children and adults with autoimmune myasthenia gravis, precautions must be taken to avoid medications that may cause worsening of myasthenic symptoms.

Infantile botulism, a disorder of the presynaptic neuromuscular junction, does not usually present in the immediate neonatal period. Onset of bulbar weakness with descending appendicular weakness and loss of reflexes raises concern for this diagnosis in an infant. Loss of the pupillary light reflex is classic but not requisite. Constipation may be an early sign. Consideration of this disorder allows for early initiation of therapy (intravenous botulism immunoglobulin; Baby-BIG). (21) Diagnosis may be supported by electrodiagnostics and, if early in the course, stool testing; in some cases, empirical treatment may be considered while test results are pending. (21)(22)

Primary Disorders of Muscle

The differential diagnosis includes congenital myopathies, congenital muscular dystrophies, congenital myotonic dystrophy, and multisystem disorders such as muscle-eye-brain disease. Key features may provide clues to examiners about subcategories of muscle disease, though there is significant overlap (Table).

TABLE. The Overlapping Features of Primary Muscle Disease Presenting in the NICU

	MYOPATHY	CONGENITAL MUSCULAR DYSTROPHY	NEUROMUSCULAR JUNCTION DISORDER	CONGENITAL MYOTONIC DYSTROPHY
Hypotonia	+	+	+	+
Eye movement abnormality	±	Not commonly	±	±
Ptosis	±	±	+ (not always)	±
Bulbar dysfunction	±	±	±	±
Creatine kinase level	Often normal	Usually elevated (not always)	Usually normal	Can be elevated
Brain malformation or hydrocephalus	±	±	–	±

The congenital myopathies are a heterogeneous group of disorders characterized by low tone, early muscle weakness, and developmental delay. Facial weakness is often prominent. The creatine kinase (CK) level is usually normal. These disorders have traditionally been classified on a histopathologic basis. Examples include core and centronuclear myopathies, congenital fiber-type proportion myopathies, and nemaline myopathies. (23) A long list of genes has been identified as causative in these disorders, and some genes have been found to be causative in more than 1 form of myopathy. Mutations in the *RYR1* gene, for example, can cause both central core disease and centronuclear myopathy. (23)(24) Limitations in eye movement (external ophthalmoplegia) may suggest centronuclear myopathy or multicore disease. Diagnosis of these disorders can be approached with a combination of genetic testing and, if needed, muscle biopsy.

Elevated CK levels (hyper-CKemia) in a hypotonic infant with early joint contracture may suggest a form of congenital muscular dystrophy, another broad category of primary muscle disease. These disorders can be variable in presentation, but the phenotype is often severe. (25) They usually have an autosomal recessive pattern of inheritance. Consideration of these disorders is important, as clinical trial opportunities may become available. Diagnosis can be approached with a combination of genetic testing using commercially available panels and muscle biopsy. Biopsy reveals dystrophic changes without the characteristic structural abnormalities seen in myopathies. (25)

Congenital myotonic dystrophy, a triplicate-repeat disorder with autosomal dominant inheritance, should be considered in the evaluation of a profoundly hypotonic infant who may have characteristic tenting of the upper lip, facial weakness, and an elongated facial/temporal atrophy. This disorder, categorized as a muscle disease, is actually a multisystem disorder. The congenital form is generally associated with more than 1,000 CTG repeats in the *DPMK* gene, inherited with anticipation and usually via the mother. (26) These neonates may have depressed mental status and are at risk for both cerebral atrophy with ventriculomegaly and hydrocephalus. The cardiac manifestations in the neonatal period include pulmonary hypertension and rarely cardiomyopathy; cardiac conduction abnormalities generally become a concern later in life. Examination of the parents (almost always the mother) may reveal distal hand/foot weakness, facial weakness with an elongated face, and grip and percussion myotonia. Clinical myotonia is absent in neonates. (26) Diagnosis is made with genetic testing.

DIAGNOSTIC TOOLS FOR ASSESSMENT

Ancillary testing can be useful when clinical examination and history do not reveal a clear cause. Some of the available diagnostic modalities are reviewed here.

Laboratory Studies

Acute hypotonia raises concern for infection. Standard cultures (blood, urine, and cerebrospinal fluid) and laboratory studies are performed as part of the evaluation for infections.

General laboratory studies to consider in the evaluation of any hypotonic infant include thyroid function tests to exclude hypothyroidism (a treatable disorder) and a screening CK level. CK levels may be elevated in congenital muscular dystrophies, but normal serum CK levels do not exclude another form of neuromuscular disorder. An elevated CK level may be repeated in case the original elevation was related to the birth process.

The possibility of an inborn error of metabolism may be supported by acidosis on basic chemistries, hyperammonemia, and persistent unexplained hypoglycemia. Further testing may include quantitative testing of urine organic acids and serum amino acids to diagnose organic acidurias and amino acidopathies. An acylcarnitine profile can be used in the diagnosis of fatty acid oxidation disorders. A very long chain fatty acid profile helps in the diagnosis of the peroxisomal disorders.

MRI of the Brain/Spine

Brain and spine MRI can exclude structural CNS etiologies of hypotonia if the clinical examination suggests CNS localization. (8)(9)(27) Imaging is performed easily and noninvasively in the neonatal period, when it can be performed without sedation. The challenge of interpreting neonatal brain imaging should be mentioned. Brain myelination begins in the fifth fetal month and continues until 2 years of age. The evolving appearance of the normal neonatal brain on MRI should be taken into account when assessing the findings.

If a brain or spinal cord etiology is suspected, MRI of the brain or spine is performed to rule out structural lesions (ie, HIE, malformation in cortical development, intracerebral hemorrhage, stroke, spinal cord tumor, paraspinal infection, a syrinx, or spinal dysraphism). (27)

EMG/Nerve Conduction Studies

Electrodiagnostics, if available, may be helpful in the assessment of the hypotonic infant, though these tests may not be available in every center. (28) Nerve conduction studies can assess for hereditary neuropathies. Because the conduction velocity of peripheral nerves does not reach adult range until 3 to 5 years of age, involvement of a clinician experienced in pediatric EMG/nerve conduction studies is important. Needle electromyography can be used to distinguish between myopathic (dystrophies, myopathies) and neurogenic (spinal muscular atrophy) processes. Repetitive nerve stimulation or single-fiber EMG may also be useful in the consideration of possible neuromuscular junction disorders.

Muscle Biopsy

Though less commonly performed in this age of readily available genetic testing, muscle biopsy plays an important role in the diagnosis of muscle disease. Congenital myopathies such as central core disease, centronuclear myopathy, nemaline myopathy, and myotubular myopathy are characterized by their unique pathologic findings on biopsy. (23)(24) It should be noted that most of these disorders are not monogenic in origin and genetic testing should be used in combination to further classify these disorders.

Targeted Genetic Testing

In addition to chromosomal studies such as karyotyping, fluorescence in situ hybridization, and microarray-based comparative genomic hybridization, use of gene panels (usually via next-generation sequencing and deletion/duplication screening when appropriate) may allow for more targeted diagnosis. (29) Whole exome sequencing (WES) is also commercially available and clinically useful in the evaluation of multisystem disorders; WES is now becoming a more commonly used tool. (30) Consultation with a geneticist is especially important when WES is considered for diagnostic purposes, (7)(8) because testing may reveal other clinically important genetic changes that may affect the patient later in life and influence the parents' future family planning decisions.

CONCLUSIONS

Hypotonia in the neonate should be considered a symptom and not a diagnosis in itself. Low tone may be a manifestation of systemic illness, dysfunction of the CNS, or a disorder of the motor unit (from anterior horn cell through the muscle fibers). In this time of rapidly expanding treatment options for previously incurable disorders, efficient and accurate diagnosis is paramount.

A focus on treatable etiologies is encouraged when creating a differential diagnosis and plan of evaluation. Infection in an encephalopathic, floppy neonate is hopefully treatable and reversible, such that an opportunity should not be missed. Metabolic disorders including urea cycle defects, organic acidurias, and amino acidopathies require treatment with specialized diets to reduce morbidity and improve developmental outcome in some cases. Acid maltase deficiency (Pompe disease), a lysosomal storage disease, can be treated with enzyme replacement, which has been found to improve both motor and cardiac function, in addition to prolonging survival. (29) Finally, the case of SMA deserves highlighting. This unrelenting, neurodegenerative disorder had been untreatable until recently; the newly available therapies have significant clinical benefit and have changed the prognosis for patients with SMA. (13)(14)

In each of these treatable disorders, early initiation of therapy improves outcome. Although the list of potential causes for neonatal hypotonia is long and unwieldy, a thorough history and careful examination can significantly narrow the differential diagnosis and allow for a targeted, efficient evaluation.

Finally, a word of caution—infants in the NICU are likely to require procedures under sedation at some point. Neuromuscular precautions for anesthesia are recommended when caring for infants with suspected muscle disease. All patients with muscle disease may be susceptible to complications such as rhabdomyolysis when exposed to certain anesthetic agents, and the possibility of myopathy/dystrophy should be shared with the anesthesiology team so that appropriate precautions can be taken.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the normal integrated (primitive) reflexes that are present in the newborn infant (such as Moro, tonic neck, rooting, and grasping) and their maturation.
- Know how a newborn infant's posture, spontaneous activity, and elicited movements are influenced by postmenstrual age and neurologic status.
- Identify the various maneuvers used to evaluate active and passive tone in newborn infants, and know how they change with maturation.
- Know the significance of persistent neuromotor abnormalities in infancy (including asymmetries).
- Recognize normal deep tendon reflexes (DTRs) in newborn infants, including unsustained clonus.
- Know the basis for (including genetic), clinical and laboratory features (including associated abnormalities), differential diagnosis, management, and outcomes of neonatal hypotonia/neuromuscular weakness.

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NeoReviews Quiz

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1. Tone is defined as the internal state of the muscle (tone is fiber tension within individual muscles and muscle groups), or the degree of muscle tension, or resistance during rest in response to stretching. Both postural (central) and peripheral tone are assessed during the normal neurologic examination of the newborn. Which of the following is CORRECT when performing an assessment of tone in a newborn?
   - A. The head position of the infant does not affect the examination.
   - B. It is necessary to assess pronation and supination to bypass the flexor predominance in the neonatal period.
   - C. In a neurologically intact term infant, the head is expected to be fully flexed backwards for 1 to 2 seconds during assessment of the head lag.
   - D. Axial tone can be assessed by evaluating slip-through with the infant in horizontal suspension.
   - E. A popliteal angle of 60 degrees is indicative of hypotonia in a term infant.
2. A 1-day-old male infant born at 39 weeks' gestational age after an uncomplicated pregnancy and delivery is transferred to your NICU for evaluation of generalized hypotonia. Which of the following findings on your neurologic examination points to upper motor neuron dysfunction?
   - A. Inability to fully bury eyelashes.
   - B. Asymmetric hyporeflexia.
   - C. Abnormal arm recoil.
   - D. Hyperreflexia.
   - E. The presence of a scarf sign.
3. You are evaluating a 1-day-old infant born at 40 weeks' gestational age for hypotonia. The pregnancy was noted to be uncomplicated with good prenatal care. The infant was delivered via spontaneous vaginal delivery, and Apgar scores were 9 and 9. Your examination reveals generalized hypotonia, areflexia, and poor suck. In addition, the infant exhibits signs of respiratory distress with tachypnea, increase in work of breathing, and paradoxical breathing. Which of the following is the most likely diagnosis?
   - A. Congenital hypomyelinating neuropathy.
   - B. Transient neonatal myasthenia.
   - C. Spinal muscular atrophy type 1.
   - D. Congenital myotonic dystrophy.
   - E. Congenital muscular dystrophy.
4. Transient neonatal myasthenia results from the postsynaptic impairment of neuromuscular transmission by transplacentally acquired antibodies in infants born to mothers affected by autoimmune myasthenia gravis. Symptoms include ptosis, hypotonia, weak cry, bulbar weakness, and respiratory difficulty or failure. What is the most common time of symptom onset in these neonates?
   - A. Immediately after birth.
   - B. Within the first 2 days after birth.
   - C. Between 72 hours and 5 days after birth.
   - D. In the second week after birth.
   - E. At age 2 to 4 months.

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5. Congenital myotonic dystrophy, a triplicate-repeat disorder, should be considered in the evaluation of a profoundly hypotonic infant with tenting of the upper lip, facial weakness, and an elongated facial/temporal atrophy. How is this condition inherited?
   - A. Autosomal dominant inheritance.
   - B. Autosomal recessive inheritance.
   - C. X-linked inheritance.
   - D. Maternal inheritance of mitochondrial DNA.
   - E. Genomic imprinting.

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The Placenta and Neurodevelopment in Preterm Newborns

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Education Gaps

1. Clinicians should recognize that preterm neonates are at risk for neurodevelopmental impairment secondary to brain dysmaturation and injury.
2. Neonatal providers should understand the implications of placental insufficiency and chorioamnionitis on the neurodevelopment of preterm neonates.

Abstract

In caring for preterm neonates, a major challenge lies in understanding the contributors to brain dysmaturation and injury, both of which serve as precursors to childhood neurodevelopmental impairment. In addition to the various adverse exposures that the preterm newborn encounters in postnatal life, the placental antecedents of preterm delivery, in and of themselves, may affect brain dysmaturation and injury. The abnormal placenta is a frequent complication of pregnancy, and placental pathologies, such as placental insufficiency and acute chorioamnionitis, often precede preterm birth.

Placental insufficiency is the principal cause of fetal growth restriction and acts via chronic fetal hypoxia. During fetal hypoxia, cardiac output redistribution to the brain represents an important fetal adaptive response; however, vascular sparing of the brain does not ensure normal brain growth. Early fetal growth restriction, which is associated with a hypermature and malperfused placenta, results in neurodevelopmental impairment independent of the duration of gestation in preterm newborns. Acute chorioamnionitis is characterized by infiltration of the placenta by immune cells and often results from infection that induces an inflammatory response. Chorioamnionitis can lead to the fetal inflammatory response syndrome and preterm labor, and thus can add to subsequent neonatal brain injury. Placental health should be assessed in understanding the origins of preterm brain dysmaturation and injury, and subsequent neurodevelopmental impairment.

Objectives After completing this article, readers should be able to:

1. Describe the features of preterm brain dysmaturation and injury.

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ABBREVIATIONS

CP	cerebral palsy
FGR	fetal growth restriction
FIRS	fetal inflammatory response syndrome
IVH	intraventricular hemorrhage
MRI	magnetic resonance imaging
PVL	periventricular leukomalacia
WMI	white matter injury

2. Discuss the pathophysiology of brain sparing in placental insufficiency.
3. Describe the pathophysiology of the fetal inflammatory response syndrome in chorioamnionitis.

INTRODUCTION

Although survival rates of very preterm neonates have risen in recent decades, reflecting incremental advances in neonatal intensive care, preterm birth continues to be a leading cause of childhood and lifelong disability. (1) The World Health Organization estimates that approximately 15 million preterm infants (1 in 10 live births) are born at less than 37 weeks' gestation worldwide every year. Among survivors of very preterm birth, which is defined as birth at less than or equal to 32 weeks, approximately 5% to 10% have major motor deficits such as cerebral palsy (CP) but a much greater proportion have cognitive, behavioral, or sensory disorders that manifest later in childhood. (2)(3) These relatively mild deficits result in academic difficulties and persist into adulthood. (4)(5) The social and economic burden of preterm birth is, therefore, considerable.

Over the last decade, the vulnerability of the preterm brain is increasingly being recognized as a problem of *dysmaturation* rather than exclusively of necrotic injuries. (6) Many groups have shown that aspects of the preterm neonate's postnatal course—including mechanical ventilation, infections, malnutrition, and painful procedures—contribute to brain dysmaturation. (7)(8)(9) Nonetheless, given that preterm birth is a syndrome that is often attributed to placental pathologies, the brain dysmaturation that leads to later neurodevelopmental impairments may have its origins in perturbed in utero physiology. There is compelling evidence that the brain of the fetus that will subsequently be born preterm is functionally altered relative to that of the fetus that will subsequently be born at term. (10) In a first-of-its-kind study of 36 pregnant women, Thomason et al showed that brain connectivity was diminished in fetuses that were subsequently born preterm, suggesting that neurodevelopmental impairment after preterm birth may have in utero origins. (10) In other words, the brain of the fetus destined to be born preterm may deviate from its normal developmental trajectory, presumably related at least in part, to the in utero environment that will eventually lead to preterm birth.

The placenta is the key tissue regulating the fetal environment, mediating the exchange of nutrients and waste products between the maternal and fetal circulations. Placental disturbances are found in many antenatal conditions that lead to preterm birth and may contribute to poor neurodevelopment (Figure). These disturbances can be broadly classified as the malperfused placenta and the inflamed placenta. The malperfused placenta, as in placental insufficiency, is a common precursor to fetal growth restriction (FGR) and preeclampsia, both of which can precede and complicate preterm birth. (11) The inflamed placenta, as in acute chorioamnionitis, is a trigger for preterm labor, and can lead to the fetal inflammatory response syndrome (FIRS) through the release of proinflammatory cytokines. (12)

A better understanding of the relationship between the placenta and neurodevelopment is necessary to fully exploit neuroprotective strategies, many of which need to begin in utero.

WHITE MATTER INJURY AND BRAIN DYSMATURATION IN PRETERM NEONATES

White matter injury (WMI) is the most common form of brain injury in preterm neonates and varies considerably in severity. WMI encompasses 2 major groups of pathology: focal necrosis, which ranges from cystic to microscopic,

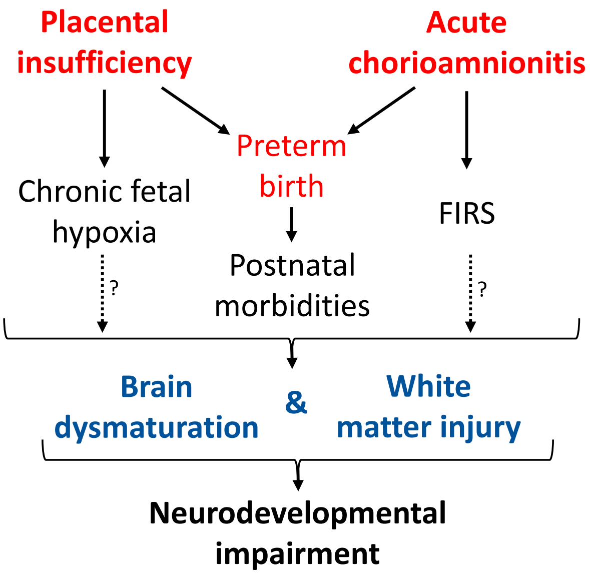

Figure. Conceptualization of the pathway from placental disturbances to neurodevelopmental impairment. FIRS=fetal inflammatory response syndrome.

and diffuse non-necrotic lesions. (13) WMI is linked in experimental models and clinical studies to ischemia, infection, and inflammation. (6) Focal cystic necrosis, the hallmark of periventricular leukomalacia (PVL), localizes to the white matter adjacent to the ventricles. These large necrotic lesions have become uncommon in contemporary cohorts of preterm neonates, and diffuse WMI is now the predominant lesion in most preterm neonates. On diagnostic magnetic resonance imaging (MRI) scans, WMI appears as areas of signal abnormalities. (14) Pathologically, diffuse WMI is marked by selective degeneration and regeneration of preoligodendrocytes, a mitotically active progenitor cell line that peaks as a cell line between 23 and 32 weeks' gestation, and then fails to mature to myelin-forming oligodendrocytes. (6) There is some suggestion that the prevalence of WMI has decreased over the last 2 decades. (15)

On diagnostic MRI, WMI represents the most easily perceived aspect of brain abnormalities in preterm neonates. However, it does not fully account for the burden of neurodevelopmental disability in this population. (14) Impaired *development* of the white matter, subcortical structures, cerebellum, and the cortex contribute more to neurodevelopmental disability after preterm birth. (9)(14) Thus, brain dysmaturation, rather than injury, is the primary brain abnormality in contemporary cohorts of preterm neonates. (6) In the white matter, developmental arrest of preoligodendrocytes prevents their maturation into myelinating oligodendrocytes and results in abnormal myelination. In the grey matter of preterm neonates, reduction in neuronal arborization and neuronal proliferation, rather than neuronal death, is implicated in reduced cortical volume. (6)

PRETERM BIRTH AND THE PLACENTA

Although preterm birth is often viewed as a single process or outcome, numerous biological mechanisms, including variants in maternal genetic loci, lead to preterm birth. (16)(17) Despite significant efforts, these etiologic pathways are poorly understood and variably classified. The most basic approach classifies preterm birth as either spontaneous or indicated. However, this schema fails to separate heterogeneous conditions. For example, preterm birth in the context of maternal hemorrhage and FGR are both considered indicated, but their antecedents and mechanisms are divergent.

In 2009, a working group brought together by the Global Alliance to Prevent Prematurity and Stillbirth Conference proposed a classification system that was based on clinical phenotypes rather than distinct etiologies. (16) Each phenotype was defined by characteristics of the pregnant woman, the fetus, the placenta, signs of parturition, and the pathway to delivery. Placental characteristics included *histologic evidence of vasculitis/infarction/necrosis* and *histologic chorioamnionitis*. (16) Using this concept of phenotype, investigators at the National Institute of Child Health and Human Development sought to group spontaneous preterm birth into 9 potential phenotypes. Two of the more common phenotypes were "infection/inflammation" and "placental dysfunction." (18) The majority of women (78%) had multiple phenotypes. Interestingly, they found that white women had more placental insufficiency than nonwhite women, and that infection/inflammation was associated with earlier spontaneous preterm birth compared with other phenotypes. However, they did not relate the phenotypes to later neurodevelopment.

It is important to consider the antenatal management of the pregnant woman at risk for preterm delivery in promoting brain health in the preterm neonate. The antenatal management of expectant preterm birth includes corticosteroids, when delivery at less than 34 weeks' gestation is anticipated within 7 days, and magnesium sulfate in the 24 hours before preterm delivery. Given the syndromic nature of preterm birth, both therapies are prescribed regardless of placental disease, and their brain-protective mechanisms are to some extent unknown.

PLACENTAL INSUFFICIENCY

Placental insufficiency is a clinical phenotype broadly characterized by maternal vascular malperfusion, placental ischemia, and chronic hypoxia. (19) Clinically, it is associated with 3 maternal-fetal conditions: preeclampsia, placental abruption, and FGR. Combined, these 3 conditions contribute to over half of medically indicated preterm births. (20) Pathophysiologically, placental insufficiency results when the maternal spiral arteries do not undergo the physiologic reduction in resistance and increase in flow necessary to perfuse the intervillous space of the placenta. (21) Early in pregnancy, the invading trophoblast remodels the uterine spiral arteries into highly dilated vessels. The placenta plays a critical role in oxygenation of the fetus and transports essential metabolites via the maternal-fetal circuit.

Placental insufficiency, as a disorder of placental function, is not defined by any single histopathologic feature. Furthermore, there is no universally accepted classification system for placental hypoxic lesions. In 2016, a consensus group from an international workshop (the Amsterdam

Placental Workshop Group) proposed a comprehensive classification system that dichotomized placental vascular processes into *maternal* and *fetal* vascular malperfusion. (22) Grossly, maternal vascular malperfusion is characterized by placental hypoplasia (placental weight ≤10th percentile for gestational age), infarction, and retroplacental hemorrhage; microscopically, it is characterized by distal villous hypoplasia and accelerated villous maturation for gestational age. Accelerated placental age for gestation is thought to be an adaptive response to chronic hypoxia, and the experience of the pathologist is of vital importance in identifying placental hypermaturation. (11)(23) Fetal vascular malperfusion likely occurs because of obstruction in fetal blood flow, and is characterized by thrombosis and segmental avascular villi. (22)

Obstetric ultrasonography can lend insight into the uteroplacental circulation and provide a measure for the severity of placental insufficiency. In the first and second trimesters, increased impedance to flow in the uterine arteries, as measured with Doppler velocimetry, predicts placental insufficiency. (24)(25) In the second and third trimesters, umbilical artery flow correlates with downstream resistance in the placental microcirculation. Current guidelines recommend the use of umbilical arterial Doppler assessment in the setting of suspected FGR, because it significantly decreases the likelihood of labor induction, cesarean delivery, and perinatal deaths. (24)(26) As placental insufficiency worsens, the fetus compensates by deliberately shunting blood away from nonessential vascular beds toward the brain, and this phenomenon is manifested by reduced resistance in the cerebral arteries. (27)

FGR refers to a fetus that has not attained its biologically determined growth potential because of a pathologic process. (28)(29) Congenital anomalies should be absent when diagnosing FGR. A recent consensus definition of FGR classified early FGR as having its onset before 32 weeks' gestation and late FGR as beginning at 32 weeks' or later, but this aspect of the definition has been inconsistently applied across studies. (29) Early FGR, rather than late, is a key concern in preterm neonates. Most, but not all, neonates born after FGR are small for gestational age, defined as having birthweights less than the 10th percentile for gestational age and sex. Importantly, not all fetuses born small for gestational age have FGR, and studies that equate the 2 populations need to be carefully interpreted. The fetus responds to chronic hypoxia by slowing its growth rate and redistributing cardiac output to the brain, heart, and adrenals. (30) Contrary to its name, "brain sparing" in FGR does not ensure normal neurodevelopment. In fact, vasodilation of the middle cerebral artery, the most commonly investigated cerebral artery in clinical fetal ultrasonography, reflects an advanced stage of fetal malperfusion and occurs following vasodilation of the other cerebral arteries. (31) Brain sparing may mitigate brain injury by conserving energy and preserving cerebral blood flow in critical regions, but it by no means ensures typical neurodevelopment. After FGR, children born at term are at increased risk for neurodevelopmental impairment and CP compared with both matched controls without FGR and children born small for gestational age with absent FGR. (32)(33) Children born preterm after FGR have a higher frequency of cognitive and learning deficits compared with children born preterm for other reasons. (34)(35) In a large French cohort study of preterm children, those born small for gestational age, which likely represented a diluted group of FGR neonates, had approximately twice the burden of cognitive and school difficulties than those born appropriate for gestational age. (34)

The main determinants of neurodevelopmental outcome in preterm FGR are the severity of placental insufficiency (as measured on obstetric ultrasonography), the gestational age at onset of FGR, and the gestational age at delivery. (36)(37) Preterm neonates with FGR who manifest in utero brain sparing are at increased risk for neonatal neurobehavioral impairment compared with those with abnormal umbilical arterial velocimetry in isolation. (38) In a subanalysis of the Trial of Umbilical and Fetal Flow in Europe, which randomized early FGR fetuses to 2 surveillance strategies, cerebral blood flow anomalies were more predictive of neurodevelopmental impairment than classic neonatal morbidities. (39) As such, in managing FGR, the degree of in utero compromise must be weighed against the adverse exposures associated with preterm delivery and neonatal intensive care in adjudicating the best time for delivery. The optimal timing for the delivery of fetuses with FGR and best means of fetal surveillance are still unknown. (28)(40)

Acquired brain injury is common in fetuses with early-onset growth restriction. (29)(41) In a prospective single center series of 90 FGR pregnancies with abnormal umbilical artery Doppler findings and delivery at 28 to 34 weeks' gestation, 40% had postnatal brain injury (ie, intraventricular hemorrhage [IVH] and PVL) compared with 12% in gestational age–matched appropriate for gestational age controls. Again, those with middle cerebral artery redistribution were at an elevated risk for brain injury. (41) Nonetheless, observational studies do not report a consistent association between IVH and FGR, with some actually suggesting that FGR is protective against IVH in preterm neonates. (42) With regard to brain maturation, the grey matter seems to be particularly vulnerable in preterm FGR neonates. Studies using MRI have shown that preterm neonates with FGR have reduced cortical grey matter volume and discordant gyrification. (43)(44) Neuropathology studies of neonates with FGR have demonstrated a reduction in the number of cortical neurons relative to controls. (45) Beyond the cortex, white matter myelination and hippocampal and cerebellar volumes are also reduced in preterm FGR. (46)

Few therapeutic options exist to reduce brain injury and dysmaturation in preterm neonates born following placental insufficiency. Daily aspirin in pregnancies at high risk for placental insufficiency reduces the frequency of FGR and is currently recommended in such scenarios. (28) In addition, when there is a real possibility of medically indicated delivery before 34 weeks' gestation, antenatal corticosteroids are indicated. (28) In the setting of placental insufficiency, however, the effects of antenatal glucocorticoids are uncertain. Observational, retrospective studies of small-for–gestational age neonates, many of whom were presumably growth restricted, have yielded conflicting results about the effects of antenatal steroids on mortality and neurodevelopmental outcomes. (47) Physiologically, several lines of reasoning suggest that FGR preterm neonates may not benefit from antenatal steroids to the same extent as those without FGR. These include elevated levels of endogenous steroids in FGR; negative effects of steroids on growth and cellular proliferation; and changes in umbilical and cerebral blood flow pursuant to antenatal steroids that may cause reperfusion injury. (47) Another potential future therapy is maternal hyperoxygenation, which has been evaluated for the management of early FGR with inconclusive results. (48)

CHORIOAMNIONITIS

Acute chorioamnionitis denotes the presence of intra-amniotic inflammation. (49) Clinically, acute chorioamnionitis refers to the constellation of maternal fever, maternal or fetal tachycardia, uterine tenderness, and foul-smelling amniotic fluid. Histopathologically, chorioamnionitis comprises diffuse infiltration of neutrophils into the chorioamniotic membrane. *Clinical* and *histologic* acute chorioamnionitis are not synonymous, and herein the term "acute chorioamnionitis" will refer to the histologic form. The rates of acute chorioamnionitis are inversely associated with gestational age at delivery. (12) Chorioamnionitis is thought to be infectious, with the microorganism ascending from the lower genital tract or emerging via the hematogenous route. However, evidence of microbial invasion is often lacking; therefore, infection is not a requisite for the diagnosis of chorioamnionitis.

Labor, be it term or preterm, is characterized by proinflammatory changes in gestational tissues. A key difference is that the inflammation associated with preterm labor is more intense than that identified in term parturition. (50) To better understand the origins of acute chorioamnionitis, it is important to appreciate the anatomic and immune compartments of the placenta. Anatomically, the placenta can be divided into the placental disc, the chorioamnion, and the umbilical cord. Immunologically, the placenta's inflammatory response can involve 2 separate immune systems: 1) maternal, with neutrophils entering the chorioamnion via decidual (ie, uterine mucosal) venules and the chorionic plate via the intervillous space, and 2) fetal, with neutrophils entering the chorioamnion and the umbilical cord via umbilical and chorionic vessels. (51) On the maternal side, the infiltration progresses from the subchorionic intervillous space to the amnion; on the fetal side, it progresses from the chorionic vessels and umbilical vein to the umbilical artery and Wharton jelly. The Amsterdam Placental Workshop Group Consensus Statement staging system for both the maternal and fetal inflammatory responses corresponds to this anatomic progression. (22) The fetal inflammatory response is also termed *funisitis* and can be accompanied by FIRS. (22)(52) FIRS is defined as an acute fetal systemic inflammatory response to chorioamnionitis. Elevated fetal cord interleukin 6, a circulating inflammatory cytokine, is indicative of FIRS. Of note, FIRS is possible in the absence of microbial infection, but the most intense response is associated with a culture-positive amniotic infection. (53)

Studies examining the association between chorioamnionitis and WMI and neurodevelopmental outcomes in children born preterm are inconclusive. (12) Variable adjustment for confounding factors including preeclampsia, and variable definitions of chorioamnionitis (ie, clinical vs histologic) may explain, at least in part, the inconsistent findings. An original meta-analysis published in 2000 found that both clinical and histologic chorioamnionitis were associated with CP and cystic PVL. (54) Although most individual studies did not identify a significant association, the pooled data found chorioamnionitis to be an independent risk factor for both CP and cystic PVL (relative risk of 1.6 and 2.1, respectively). The most recent meta-analysis published in 2017 distinguished preterm and term cases and forward (determining the rate of CP in patients with and without chorioamnionitis) and backward (determining the rate of chorioamnionitis in patients with and without CP) approaches to analysis. (55) These authors reported an association between histologic chorioamnionitis and CP in children in preterm cohorts (ie, forward approach). The association between clinical chorioamnionitis and CP was limited to cohorts of children with CP (ie, backward approach); results from studies using the backward approach are more susceptible to distortion from bias and confounding. A recent multicenter study examining the association between histologic chorioamnionitis and IVH, WMI, and later cognitive and motor scores found that once perinatal factors were accounted for in the regression model, chorioamnionitis was not strongly associated with any of the outcomes. (56) Unfortunately, few studies have distinguished between chorioamnionitis affecting the fetal side of the placenta, capable of instigating FIRS, and that affecting the maternal side. One recent study correlated the severity of funisitis with neurodevelopmental impairment, with necrotizing funisitis and severe chorionic vasculopathy being associated with the highest frequency of impairment. (57)

Chorioamnionitis has also been linked to white matter dysmaturation in some studies but not others. (58)(59) The association between histologic chorioamnionitis and white matter microstructural development at term-equivalent age independent of postnatal factors has been inconsistent, and whether white matter dysmaturation begins in utero requires further attention. (58)(59) In a mouse model of perinatal WMI, moderate systemic inflammation blocked oligodendrocyte maturation, resulting in persistent myelination defects. (60) Mechanistically, FIRS may contribute to white matter dysmaturation, and later neurodevelopmental impairment, via proinflammatory cytokines. (12) The cytokines can increase the permeability of the blood-brain barrier to leukocyte infiltration. Preoligodendrocytes are particularly vulnerable to inflammation; inflammatory insults such as postnatal sepsis, bronchopulmonary dysplasia, and necrotizing enterocolitis are strongly associated with white matter dysmaturation and later impairment. (12) A reduction in epigenetic modifications to the oligodendrocyte lineage induced by inflammation may predispose these children to further damage and prevent regeneration; recapitulating developmental epigenetic changes could be a viable therapeutic pathway in the future. (61)

FUTURE AREAS FOR RESEARCH

To mitigate the harm associated with placental insufficiency and chorioamnionitis, a better understanding of the in utero antecedents of postnatally detected brain dysmaturation and injury is needed. To that effect, in utero assessment of placental and brain development (and maldevelopment) could help elucidate the upstream, placenta-mediated origins of brain dysmaturation that precede adverse exposures in the NICU. Ultrasonography, the primary tool for placental and brain evaluation in utero, is limited by field of view and tissue resolution. Advanced MRI techniques for the placenta and fetal brain hold promise in identifying the pathophysiologic consequences of the disordered placenta. (62)(63) MRI of the placenta can provide important real-time structural and functional information to interrogate the multiple facets of placental pathology. Apparent diffusion-coefficient maps can identify and quantify areas of accelerated and restricted diffusion that correspond to areas of necrosis, infarction, or fibrosis in the placenta. (64) Fetal brain MRI could identify prenatal brain dysmaturation, quantify fetal cerebral blood flow and oxygen extraction, and facilitate the optimization and development of fetal neuroprotective strategies. (10)(63) The development of the artificial placenta as an extrauterine support system adds more urgency to understanding in utero brain health. (65) Transfer from the womb to the artificial placenta would preferably be accomplished before brain health is put at risk. In utero quantitative brain imaging could be used to evaluate candidates for transfer from the womb to the artificial placenta. Furthermore, in utero quantification of cerebral blood flow and oxygen extraction by MRI could serve as biomarkers for response to potential therapies.

In summary, in utero MRI could isolate processes that begin in utero, before postnatal insults occur, and elaborate the effects of placental malperfusion and inflammation as they relate to brain health.

CONCLUSIONS

The influence of the placenta on the brain health of preterm neonates is central to understanding the neurodevelopmental outcomes in this population, and calls for closer interaction between fetal-maternal medicine specialists, neonatologists, and neurologists. In preterm neonates, placental insufficiency and chorioamnionitis influence later neurodevelopment, especially when they occur together. (66) Both placental insufficiency, via inadequate oxygen and nutrient delivery, and chorioamnionitis, via FIRS, may contribute to brain dysmaturation and injury and may establish a foundation for postnatal contributors to brain health. Advanced brain imaging can now be applied to establish the substrates responsible, at least in part, for the adverse neurodevelopmental outcomes related to these hostile in utero environments. At present, therapies to attenuate the burden of impairment consequent to placental malperfusion and inflammation in the preterm neonate are limited. Advances in research methods, including in utero brain imaging, provide an unprecedented opportunity to identify new ways to improve the brain health of preterm neonates, even before delivery.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the complications and effects of chorioamnionitis in the mother and the fetus.
- Know the causes and pathophysiology, including cellular abnormalities, of chronic asphyxia syndromes (eg, chronic fetal hypoxia and placental insufficiency).
- Know the risks of neurodevelopmental impairments in term infants, late preterm infants, moderately preterm infants, and extremely preterm infants, with and without neurologic risk factors.

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1. A female preterm infant born at 25 weeks' gestational age is now 14 weeks old. She received mechanical ventilation for 2 weeks in the initial newborn period, had feeding intolerance with slow advancement, but is now tolerating feedings. The infant has poor oral feeding ability and also has abnormalities on neurologic examination. A magnetic resonance imaging scan of the brain reveals some white matter injury. Which of the following correctly describes this type of injury?
   - A. White matter injury is the most common form of brain injury in preterm infants.
   - B. Large necrotic lesions adjacent to the ventricles are the most common manifestation.
   - C. White matter injury reflects necrosis of fully developed oligodendrocytes.
   - D. White matter injury is closely linked to ischemia, but not to infection or inflammation.
   - E. Although white matter injury can sometimes be seen on magnetic resonance imaging, the optimal imaging modality is ultrasonography.
2. A male fetus is being followed for growth restriction. He is delivered at 30 weeks' gestational age because of ongoing concerns for growth restriction and placental insufficiency. The placenta is examined by the pathologist. Which of the following is most likely to be a finding?
   - A. Larger than average placental size accounted for by overcompensation of blood flow.
   - B. Distal villous hyperplasia and hypertrophy.
   - C. Retroplacental hemorrhage and infarction.
   - D. Characteristics of immature and undeveloped placenta.
   - E. A consistent finding of velamentous cord insertion.
3. A woman who had preeclampsia and preterm birth in her prior pregnancy is receiving prenatal care for a subsequent pregnancy. She is receiving serial ultrasound evaluations. Which of the following findings are consistent with relatively severe placental insufficiency?
   - A. Normal blood flow and normal placental appearance during the first and second trimesters.
   - B. Decreased impedance to flow in the uterine arteries.
   - C. No significant findings on umbilical arterial Doppler assessment.
   - D. Increased resistance in fetal cerebral arteries.
   - E. Shunting of blood away from nonessential vascular beds toward the fetal brain.
4. A male fetus is being followed for growth restriction. The mother is receiving close follow-up for prenatal care and serial ultrasound evaluations. Which of the following statements concerning fetal growth restriction is correct?
   - A. Fetal growth restriction is synonymous with small for gestational age.
   - B. When the brain is "spared" from growth restriction, there can be reassurance with regard to normal neurodevelopment.
   - C. Children born preterm after fetal growth restriction have a higher frequency of cognitive and learning deficits compared with children born preterm for other reasons.
   - D. Aspirin given in the context of placental insufficiency can exacerbate bleeding risk and increase the severity of growth restriction.
   - E. The growth-restricted fetus preferentially redistributes cardiac output primarily to the kidneys, leading to oligohydramnios.

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5. A pregnant woman presents in preterm labor at 28 weeks of gestation. She receives tocolytics and steroids, but proceeds to deliver her infant the day after admission. On pathologic examination, the placenta is noted to have histologic evidence suggesting chorioamnionitis. Which of the following statements concerning this diagnosis is correct?

   A. Documented maternal or neonatal fever is necessary to confirm a diagnosis of chorioamnionitis.
   B. The rates of acute chorioamnionitis are inversely associated with gestational age at delivery.
   C. Evidence of microbial invasion in histology is necessary for a true diagnosis of chorioamnionitis.
   D. The primary histologic finding in chorioamnionitis is infiltration of the placenta by maternal lymphocytes and monocytes.
   E. Chorioamnionitis has been associated with white matter brain injury and cerebral palsy, but only in the context of term births, not preterm births.

The Placenta and Neurodevelopment in Preterm Newborns

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Neonatal Hydrocephalus

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Education Gaps

1. Hydrocephalus is a significant risk factor for future neurodevelopmental impairment in both preterm and term infants. However, the evidence informing the optimal timing of interventions for infants with evolving hydrocephalus is inadequate.
2. A number of interventions to reduce intracranial pressure exist, but there is practice variation among treating clinicians. Results from recent clinical studies have begun to inform choices among the various interventions.

Abstract

Hydrocephalus is one of the most common congenital abnormalities affecting the nervous system, occurring in 0.3 to 2.5 per 1,000 live births. It results from obstruction of cerebrospinal fluid (CSF) pathways by a diverse range of developmental, genetic, and acquired abnormalities and can have negative consequences on the neurodevelopmental outcome of affected neonates. Historically, hydrocephalus was diagnosed after birth and managed with a shunt procedure; however, with the advent of advanced antenatal imaging techniques, it may now be detected and treated before delivery in some individuals. Moreover, surgical options for the treatment of hydrocephalus have increased over the past few decades, and temporary CSF diversion may prevent the need for permanent shunt placement. Posthemorrhagic hydrocephalus is the most common cause of hydrocephalus in the preterm newborn, but the timing of surgical intervention for this condition remains controversial. Recent evidence suggests that earlier, rather than later, intervention may have some benefits, but more data are needed to adequately inform clinical practice. Regardless of etiology or timing of diagnosis, a thorough understanding of the natural history of hydrocephalus and the range of treatment options available is needed for parental counseling, prognostication, and appropriate surgical management.

Objectives

After completing this article, readers should be able to:

1. Understand the pathophysiology of hydrocephalus.
2. Recognize the clinical symptoms of increased intracranial pressure.

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ABBREVIATIONS

BEH	benign external hydrocephalus
CPC	choroid plexus cauterization
CSF	cerebrospinal fluid
ETV	endoscopic third ventriculostomy
EVD	external ventricular drain
ICP	intracranial pressure
IVH	intraventricular hemorrhage
LP	lumbar puncture
MMC	myelomeningocele
MRI	magnetic resonance imaging
PHH	posthemorrhagic hydrocephalus
VAD	ventricular access device

3. Formulate a management approach for a patient with evolving hydrocephalus.
4. Appraise interventions to reduce intracranial pressure based on current evidence and recognize practices that are not beneficial.

INTRODUCTION

Hydrocephalus is a clinical diagnosis of cerebrospinal fluid (CSF) accumulation in the ventricles and brain spaces accompanied by an increase in intracranial pressure (ICP). CSF is a clear, colorless liquid that nourishes the neural tissue and removes toxic metabolites. The choroid plexus (of the lateral ventricles) and the tela choroidea (of the third and fourth ventricles) produce 70% of the body's CSF; the remainder is secreted by the ependymal epithelium and blood-brain barrier capillaries. (1) CSF production begins by the sixth week of gestation and approximately 300 to 500 mL of CSF is produced daily in the neonate. The CSF travels from the lateral ventricles to the third and fourth ventricles via the foramen of Monro and the cerebral aqueduct, respectively (Fig 1). It then enters the subarachnoid space surrounding the cerebral hemispheres and spinal cord. The superior sagittal sinus of the dural venous system has arachnoid granulations (or villi) to absorb CSF, which then further circulates to the internal jugular veins and inferior vena cava. (1) Arachnoid villi become visible between 6 and 18 months of age and increase in number and size over the first few years of age. CSF is continuously produced as it is absorbed, and there is a delicate balance between rates of CSF production and absorption.

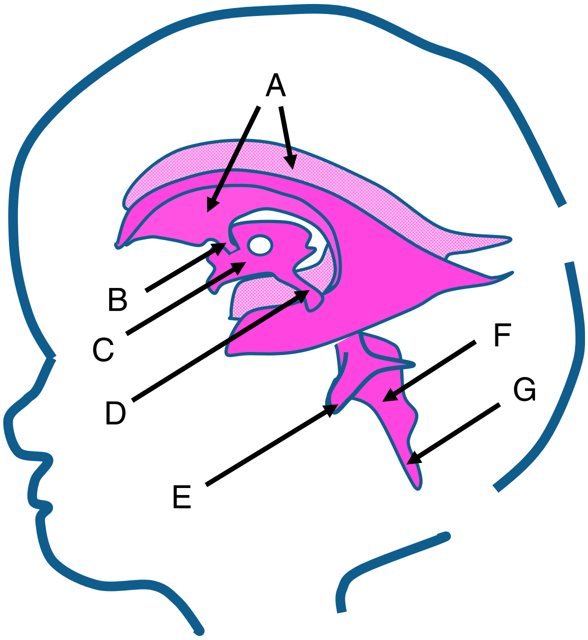

Figure 1. Illustration of the ventricular system. A. Lateral ventricles. B. Foramen of Monro. C. Third ventricle. D. Cerebral aqueduct. E. Foramen of Luschka. F. Fourth ventricle. G. Foramen of Magendie.

The mechanism by which the accumulation of CSF in hydrocephalus leads to brain injury is not fully understood. When alterations in CSF flow dynamics (most commonly due to obstruction in the CSF circulatory pathway) gives rise to ventriculomegaly, the developing brain may be affected in several ways. Increased intraventricular pressure distends and compresses periventricular tissue, and this may result in ischemia, hypoxia, and cerebral edema. Hydrocephalus can also bring about changes in brain cytoarchitecture, structure, and metabolism. These changes may progress to altered blood-brain barrier transport as well as reduced amyloid clearance, dendritic and synaptic changes, and neuronal cell death. While the effect of apoptosis in the cerebral cortex is mitigated by the sheer number of cortical neurons, oligodendrocyte injury can result in demyelination, axonal degeneration, and gliosis with adverse effects on motor, behavioral, cognitive, and neurodevelopmental outcomes. (2)

RISK FACTORS/ETIOLOGY

Neonatal hydrocephalus is broadly categorized as congenital or acquired (Fig 2). Congenital hydrocephalus is further categorized as syndromic or isolated/nonsyndromic based on whether or not the hydrocephalus is part of an underlying genetic syndrome.

Congenital Hydrocephalus

Genetic forms of hydrocephalus are rare, but the most common form is X-linked recessive hydrocephalus (Fig 3). This is a family of related entities, collectively known as "L1 disease," that result from mutations in the *Xq28* gene encoding *L1CAM* (L1 protein). These conditions include HSAS (*h*ydrocephalus due to congenital *s*tenosis of the *a*queduct of *S*ylvius), MASA syndrome (*m*ental retardation, *a*phasia, *s*huffling gait, *a*dducted thumbs), spastic paraparesis type 1, and X-linked agenesis of the corpus callosum. The L1 protein is part of a superfamily of neuronal cell adhesion molecules expressed on the axons of developing

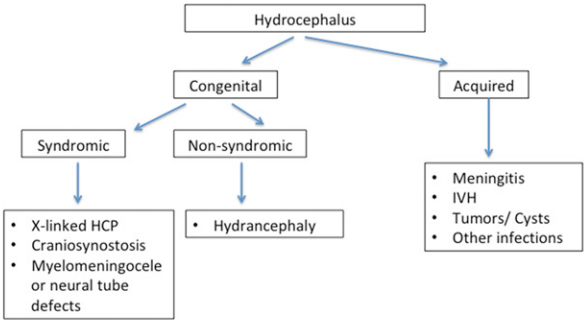

Figure 2. Categorization of neonatal hydrocephalus (HCP). IVH=intraventricular hemorrhage.

neurons. (3) Together, the estimated incidence of these syndromes is 1 in 25,000 to 60,000 males, and L1 disease is thought to play a role in up to 25% of isolated congenital hydrocephalus in males. (4) Unfortunately, infants with L1 disease often have severe developmental delay, even with early CSF diversion. Hydrocephalus may also be present in conditions affecting chromosomes 8, 9, 13, 15, 18, and 21.

Although not genetic in nature, the association of hydrocephalus with open neural tube defects such as myelomeningocele (MMC) is well known and is a common cause of congenital syndromic hydrocephalus. Approximately 90% of infants with MMC develop hydrocephalus from Chiari malformation type II and require CSF diversion. (5) The "unified theory" proposes that an in utero open neural tube causes leakage of CSF that prevents appropriate accumulation of CSF in the embryonic ventricles. This, in turn, leads to abnormal development of the posterior fossa and subsequent descent of the cerebellum, brainstem, and fourth ventricle through the foramen magnum. (6) The descent interrupts CSF flow with resultant hydrocephalus. The Management of Myelomeningocele Study trial compared outcomes of prenatal and postnatal MMC repair; it was noted that infants who underwent fetal repair were half as likely to need a ventricular shunt (40% vs 82%), were less likely to develop Chiari malformation, and had better neuromotor outcomes with higher rates of ambulation at 30 months of age. (7) Based on these results, prenatal repair of MMC is considered to be the standard of care in centers with fetal surgery expertise. Vigilant screening of mothers with prenatally diagnosed MMC can help identify infants who may benefit from this complex and challenging intervention.

Hydranencephaly is the archetypical cause of nonsyndromic congenital hydrocephalus, occurring in 1 in 10,000 births. Although several causes have been proposed, the most common is intrauterine bilateral carotid artery occlusion with subsequent infarction of all cerebral tissue supplied by the anterior circulation and obliteration of the cerebral hemispheres. (8) On neuroimaging, the meninges and skull are intact and the empty cranial cavity is filled with CSF. The vertebrobasilar circulation is spared, preserving the thalamus, brainstem, and cerebellum (Fig 4). In newborns with seizures who have not been prenatally diagnosed, the absence of electrical activity on postnatal electroencephalography with the exception of occipital spikes is suggestive of hydranencephaly. (9) Prognosis is extremely poor and most infants die within the first year after birth. For this reason, treatment is largely symptomatic and supportive. Distinguishing hydrancephaly from maximal hydrocephalus is important for prognostication. In the latter, the cortical mantle is severely stretched and distorted but is preserved and has the ability to develop and regain function after appropriate CSF diversion.

Acquired Hydrocephalus

Acquired hydrocephalus occurs after the development of the brain and ventricles and is the result of secondary mechanisms such as infection (*t*oxoplasmosis, *o*ther agents,

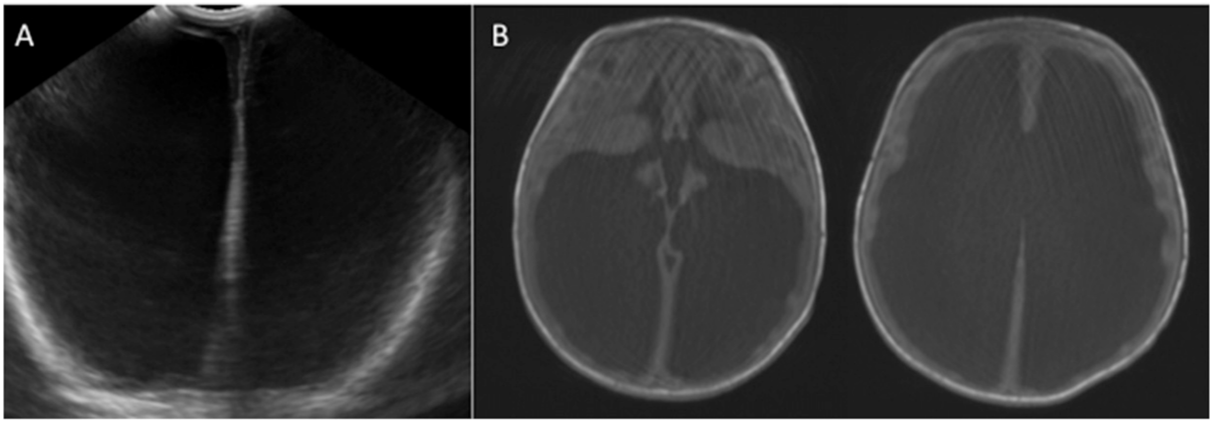

Figure 3. A. Cranial ultrasound scan (axial plane). B. Magnetic resonance imaging scan (axial plane) of an infant with X-linked hydrocephalus.

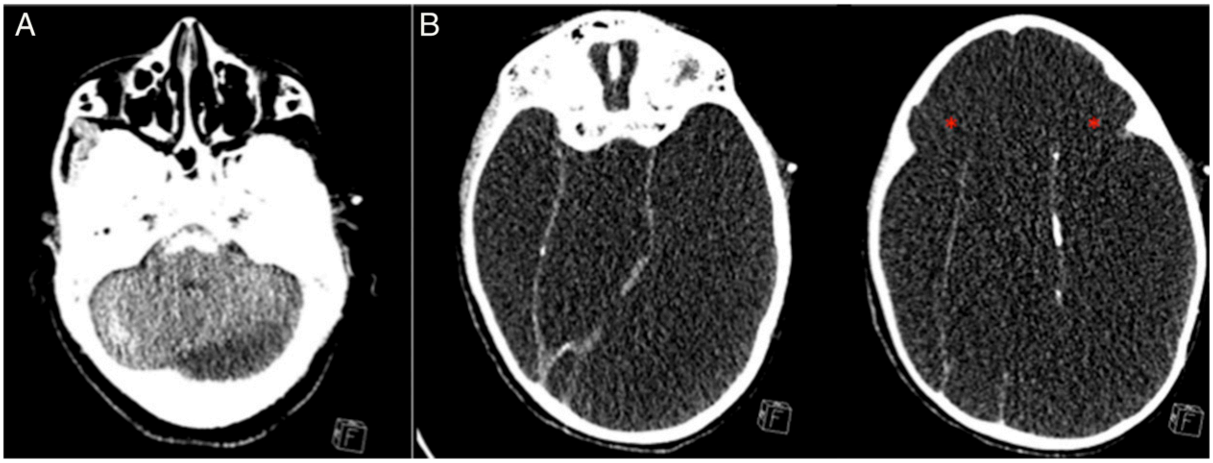

Figure 4. Head computed tomographic scan (axial plane) of an infant with hydranencephaly. Note the absence of the frontal lobe in this form of congenital hydrocephalus (marked by red stars), which distinguishes it from maximal hydrocephalus.

*r*ubella *c*ytomegalovirus, and *h*erpes simplex [TORCH], tuberculosis, or bacterial meningitis), intraventricular hemorrhage (IVH), trauma, and structural abnormalities (tumors or cysts). These secondary causes impair CSF absorption and/or lead to obstruction, particularly at the aqueduct. Infections, specifically cytomegalovirus or toxoplasmosis may result in cerebral atrophy and inflammation of arachnoid granulations, impairing CSF absorption. IVH can lead to both scarring at the aqueduct and impaired absorption at arachnoid granulations.

By far, the most common cause of hydrocephalus in the neonatal population is IVH resulting in posthemorrhagic hydrocephalus (PHH). Neonatal PHH occurs in 15% to 35% of preterm infants with IVH. The vascular supply to the germinal matrix of preterm infants, particularly those born at less than 34 weeks' gestation, is not invested with supporting stroma. This confers vulnerability of blood vessels in this area to rupture with increased pressure passive cerebral blood flow, which may occur during periods of cardiovascular instability and during resuscitation. Intraventricular blood induces an inflammatory cascade that leads to permanent remodeling and scarring of ventricular walls, with subsequent impairment in CSF flow and absorption. Although the risk factors for IVH are relatively well established— prematurity, low birthweight, and cardiovascular instability—the factors that influence which infants develop PHH are not as well understood. (10)(11) As with other types of hydrocephalus, PHH results in increased cerebrovascular resistance, decreased cerebral perfusion, and stretching and compression of brain parenchyma.

Additional causes of acquired hydrocephalus result from any abnormality that involves obstruction at the outlet of the fourth ventricle, the foramen magnum, or the tentorial notch. Posterior fossa tumors or cysts (arachnoid, colloid) can physically obstruct normal CSF flow. These may be congenital or acquired. Tectal gliomas that obstruct the aqueduct of Sylvius are not usually present in the neonate. Choroid plexus papillomas can present in the neonatal period and lead to hydrocephalus because of both obstruction and overproduction of CSF in the choroid plexus. Dandy-Walker malformation and its variants account for 2% to 10% of children with hydrocephalus. It is defined as hypoplasia of the cerebellar vermis with cystic dilation of the fourth ventricle. Hydrocephalus occurs because the posterior fossa cyst seen in this syndrome does not always communicate with the fourth ventricle outlet. Similarly, congenital aqueductal stenosis or membranous obstruction of the aqueduct can also result in hydrocephalus. It accounts for 20% of cases of hydrocephalus detected in fetuses. Blockage at the aqueduct is suspected when the lateral and third ventricles are enlarged, but the fourth ventricle is small. Identification of the anatomic site and cause of CSF obstruction is critical in determining the appropriate treatment. Some neonates may have a temporary absorptive problem and only require temporary CSF diversion, while others may need long-term shunting.

"Benign" external hydrocephalus (BEH) is a unique entity with less potential for adverse neurodevelopmental outcomes. It is defined by enlarging subarachnoid spaces, often over the frontal lobes, with normal or moderately enlarged ventricles and macrocephaly. On neuroimaging, there may be a widened interhemispheric fissure as well as an enlarged third ventricle and basal cisterns. It is usually diagnosed after 6 months of age and is rarely observed in newborns. An important distinction from true hydrocephalus is that BEH is not associated with increased

ICP or associated clinical features. The macrocephaly associated with BEH is usually self-limited and typically normalizes after 1 year of age. It is therefore often managed expectantly and only rarely requires shunting or medical therapy. Some affected children have hypotonia and neurodevelopmental delays, particularly in gross motor functioning, though most of these children later catch up to their peers. Although BEH is idiopathic in most cases, it has been reported in the context of prematurity, meningitis, high venous pressure from cardiac dysfunction, and trauma. (12) It has been theorized that BEH may be related to immature arachnoid villi that are transiently unable to adequately absorb CSF. Approximately 40% of children with BEH have at least 1 relative with a head circumference in the 95th to 98th percentile. (13) Familial BEH is thought to have an autosomal dominant or multifactorial mode of transmission. (14) BEH is also associated with several other conditions including craniosynostosis, achondrodysplasia, Sotos syndrome, and glutaric aciduria type 1.

PRESENTATION

Clinical signs of hydrocephalus in the preterm or full-term infant are secondary to increased ICP and include a bulging fontanelle, splayed sutures, prominent scalp veins, irritability, lethargy, poor feeding, recurrent vomiting, high-pitched cry, seizures, and “sunsetting” eyes. The sunsetting appearance of the eyes, with upgaze paresis and downward displacement, results from excessive CSF pressure on the suprapineal recess of the midbrain and periaqueductal structures. Papilledema may be seen on ophthalmologic examination. In neonates, increasing CSF pressure affects the flexible skull and prevents appropriate fusion of the skull bones along suture lines, resulting in macrocephaly. A head circumference that enlarges rapidly in the neonatal period or is later observed to cross percentiles on a growth chart warrants a thorough evaluation with neuroimaging.

EVALUATION

Prenatal diagnosis of hydrocephalus can be accomplished by fetal ultrasonography or magnetic resonance imaging (MRI). However, MRI is superior to ultrasonography in delineating neuronal myelination and any associated cerebral malformations. Specific MRI sequences to compensate for fetal movement are now available and allow for more precise evaluation of brain development and ventricular size. When measured with MRI, ventricle sizes are often larger than those observed on ultrasonography by 1 mm. (15) On fetal imaging, the transverse atrial width, often referred to as the atrial diameter, is the most useful measurement. An atrial diameter of less than 10 mm is considered normal. A width of 10 to 15 mm is diagnosed as mild to moderate ventriculomegaly, of which 14% progress to hydrocephalus, 57% remain stable, and 29% regress spontaneously. (16) A width of more than 15 mm is considered severe ventriculomegaly. (17) Ventriculomegaly seen on fetal imaging does not always result in a postnatal diagnosis of hydrocephalus as it may result from in utero destruction or maldevelopment of periventricular structures rather than hydrocephalus per se. Therefore, it is important to discern the etiology of fetal ventriculomegaly to best predict outcome and guide antenatal treatment.

Postnatal diagnosis and surveillance of hydrocephalus can be accomplished using cranial ultrasonography to assess ventricle size and serial head circumference measurement. Again, true hydrocephalus must be distinguished from “hydrocephalus ex vacuo,” which refers to compensatory enlargement of the cerebral ventricles and/or subarachnoid spaces without increased ICP. The latter is usually due to encephalomalacia and/or periventricular volume loss that has occurred in the setting of stroke. The open anterior fontanelle in newborns permits facile measurement of ventricle size using head ultrasonography; serial head ultrasonography is a more reliable surveillance tool than head circumference measurements.

Methods to standardize postnatal ventricle size measurements have been proposed by several groups. Levene defined the ventricular index as the distance from the wall of the lateral ventricle to the falx at the midcoronal level. (18) Growth curves for the progression of this index have served as the basis for timing of interventions in several studies. (19) Davies et al developed additional measures that evaluate ventricle size at multiple locations, which is plotted on standard curves to address the asymmetric ventricular dilation often seen in infants. (20) Finally, others have presented measures of ventricle size that are normalized to head utilization ratios at the frontal and temporal horn levels (fronto-occipital horn ratio and frontotemporal horn ratio). This approach has high inter-rater reliability and validated norms. (21)(22)

MANAGEMENT: SHUNT APPROACH, TIMING, RATIONALE

The mainstay of management of hydrocephalus is the relief of increased CSF and ICP. A number of medical and surgical strategies have been proposed and studied. We refer the reader to an excellent 10-part systematic review and evidence-based guidelines published for the management of pediatric hydrocephalus in the *Journal of Neurosurgery: Pediatrics*. This review includes the optimal treatment strategies for the management of PHH in the preterm neonate. (23) Decreasing CSF production with diuretics (either furosemide or acetazolamide) has been ineffective and potentially unsafe. (24)(25)(26) Similarly, use of intraventricular fibrinolysis in the setting of PHH has been explored in small studies with disappointing results and notable safety concerns. (26)(27) As a result, neither diuretics nor thrombolysis are recommended as treatments for PHH in preterm newborns. (23)

The remaining options involve surgical diversion of CSF. Decompression of the ventricles with a temporary device is often undertaken first, especially for small infants or when it is not clear if permanent shunting will be required. If the underlying hydrocephalus does not resolve, the temporary device may be removed and replaced with a fully internalized cerebral shunt. The precise timing of temporary and permanent CSF diversion in preterm neonates is still relatively controversial (23); only recently has there been a movement to formally standardize this intervention using an infant's weight, ventricle size, and other specific clinical parameters. (28)(29)(30)(31) Moreover, results have been mixed with respect to benefits of early, aggressive intervention. A recent observational study in preterm infants of early versus late intervention (defined by ventricular index) showed that infants receiving early intervention had better outcomes that those with late intervention, even if they later required permanent shunting. The authors concluded that early intervention appears to outweigh potential risks. (31) However, data from a recent randomized trial of early versus late intervention (defined by ventricular index) did *not* show improvements in the composite outcome of permanent shunt placement or death. Neurodevelopmental outcomes for these patients are currently pending. (30) Additional randomized controlled trials are needed to help inform this important clinical question.

Temporary CSF Diversion

A number of temporary CSF diversion methods are available and used in neonates: ventricular access device (VAD), external ventricular drain (EVD), ventriculosubgaleal shunt, and serial lumbar punctures (LPs) (Fig 5). CSF may be aspirated by way of a VAD, EVD, or LP. An EVD is particularly helpful in diverting CSF in the acute stage of meningitis, and permits serial CSF sampling for culture. A VAD has less morbidity and mortality when compared with an EVD as well as a lower risk of infection when repeated CSF aspiration is undertaken. (32)(33)(34)(35)(36) Ventriculosubgaleal shunts may reduce the need for daily CSF aspiration. (37) A large, prospective study showed that ventriculosubgaleal shunts decrease the need for permanent CSF diversion. (38) Serial LPs are an effective, immediate treatment for elevated ICP but do not obviate the need for permanent CSF diversion; furthermore, they may contribute to infection. (23)(24)(25) Regardless of the specific mode, early CSF diversion is associated with a reduced need for permanent shunting and reduced risk of moderate-to-severe disability. (31)

For patients with PHH, temporary diversion and decompression may relieve ICP but does not address the pathophysiologic cascade following hemorrhage that contributes to chronic hydrocephalus. One approach that has been explored is temporary drainage and continuous irrigation of the ventricles with artificial CSF and a fibrinolytic agent (DRIFT therapy). (27) The original trial did not demonstrate a difference in the primary outcome of death or the need for a shunt and showed increased occurrence of secondary hemorrhage. However, follow-up of the cohort at later ages showed some improvement in developmental outcomes, suggesting that this intervention may warrant further exploration. (39) Current guidelines do not support use of this therapy. (23)

Permanent CSF Diversion: Shunts

The goal of CSF diversion is to establish a permanent communication between the ventricular CSF and a distal anatomic space. The most common distal destination for CSF diversion is the peritoneum because of the large absorptive surface of the peritoneal lining (ventriculoperitoneal shunt). However, in patients who suffer from peritoneal pathologies (ie, necrotizing enterocolitis, abdominal ascites, peritoneal dialysis), diversion into the atria of the heart (ventriculoatrial shunt) or the pleural cavity (ventriculopleural shunt) may be necessary (Fig 6). Lumboperitoneal shunts are not typically used in neonates.

Shunts typically consist of a few parts: an inflow catheter connected by a valve mechanism to an outflow catheter. The inflow catheter begins at the ventricle or subarachnoid space, exits the skull, and travels under the skin to the chosen diversion site. A valve mechanism controls pressure and CSF flow through the tubing and is usually placed on the top of the head or behind the ear. Shunts may also include reservoirs for CSF sampling and/or medication administration.

Permanent CSF Diversion: Endoscopic Third Ventriculostomy

Endoscopic third ventriculostomy (ETV), with or without choroid plexus cauterization (CPC), is a safe procedure with varying degrees of success in the treatment of neonatal

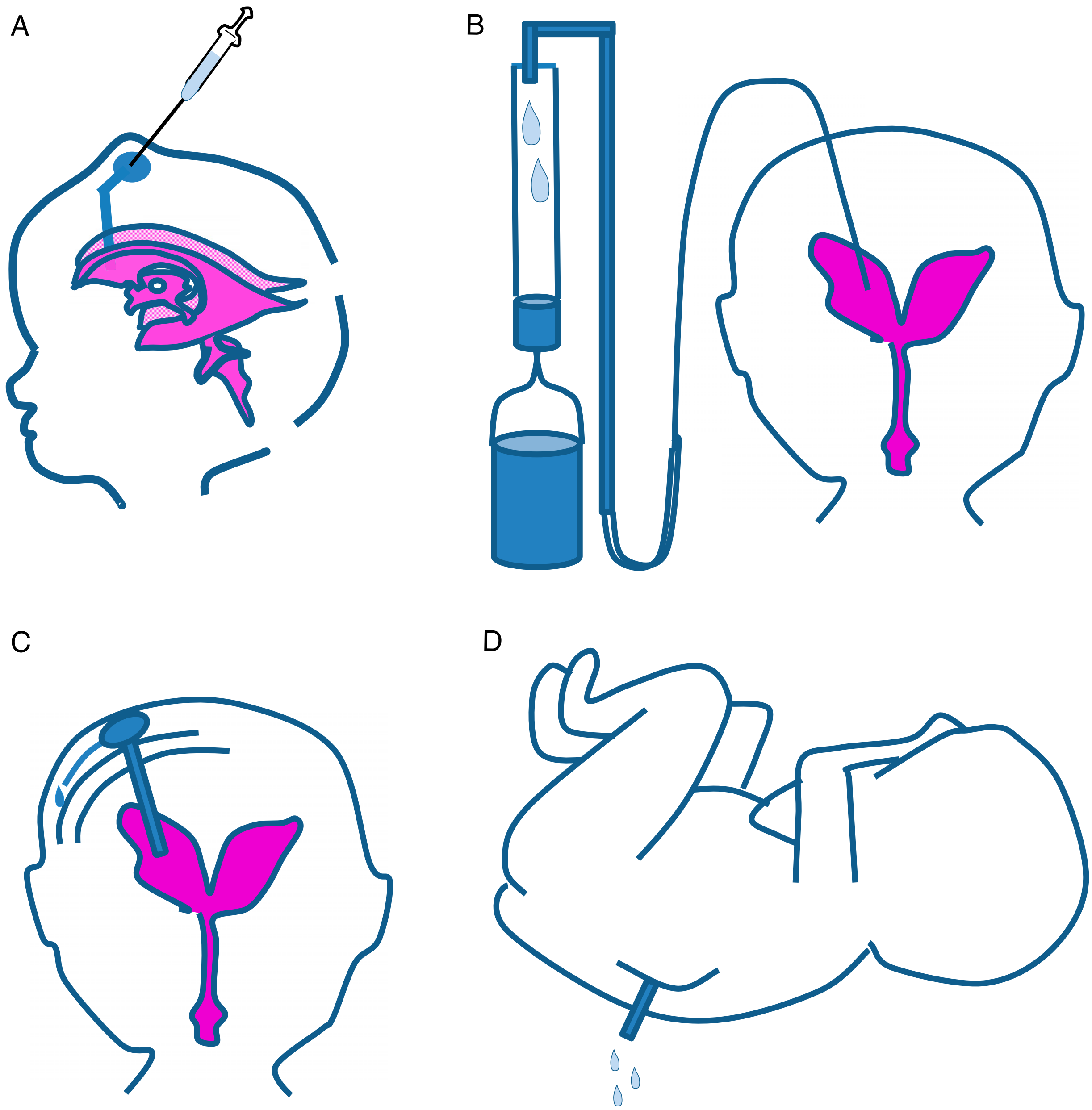

Figure 5. Forms of temporary cerebrospinal fluid (CSF) diversion. A. Ventricular access device (VAD). A needle is shown to represent CSF aspiration from the VAD. B. External ventricular drain. C. Ventriculosubgaleal shunt. D. Lumbar puncture.

hydrocephalus. It involves unilateral coronal suture entry to the third ventricle, followed by fenestration of the floor of the third ventricle, to allow CSF to be internally diverted to the basal cisterns and reabsorbed by arachnoid granulations. A rigid or flexible endoscope can be used, and an EVD is inserted for postoperative CSF diversion at the discretion of the operating surgeon. When performed successfully, the ETV stoma allows for an alternative route of CSF flow in obstructive hydrocephalus (Fig 6). Established predictors of ETV and CPC success are older age and greater degree of CPC. (40) It is thought that ETV is more successful in older infants as a result of restoration of CSF absorption at a later age. The ETV Success Score is a validated clinical prediction tool for estimating operative success based on age at surgery, cause of hydrocephalus, and previous history of shunt. (41)

Risks of ETV/CPC include vascular injury, neural structure injury, endocrine or electrolyte dysfunction, CSF leak, and infection. The volume of irrigation during an ETV must be monitored because excessive irrigation can contribute to cerebral herniation and cardiovascular compromise. Intraoperative injury can occur to the fornix, thalamus,

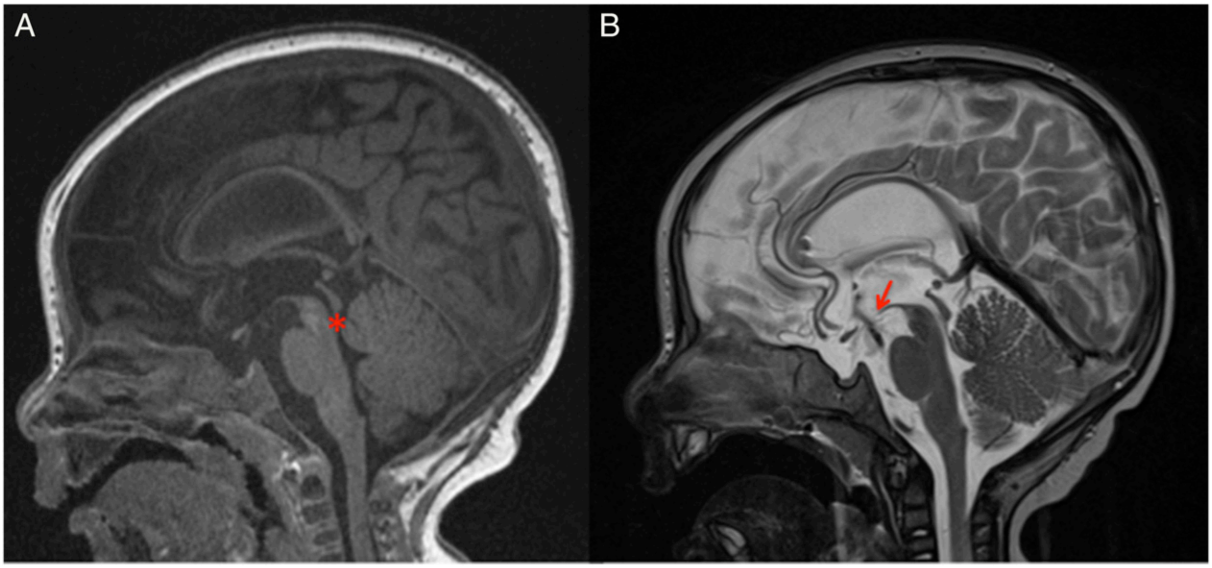

Figure 6. Brain magnetic resonance imaging scan of an infant with aqueductal stenosis before and after endoscopic third ventriculostomy (ETV). A. Preoperative sagittal T1; red star indicates site of aqueductal stenosis. B. Postoperative sagittal cerebrospinal fluid (CSF) flow study; red arrow indicates site of ETV stoma with CSF flow visualized.

hypothalamus, or oculomotor nerve and may be catastrophic. Transient ocular divergence and anisocoria sometimes occur postoperatively because of midbrain stretch. Manipulation or injury to the tuber cinereum during an ETV can result in cerebral endocrine dysfunction with transient or permanent diabetes insipidus. Given this risk, postoperative monitoring of electrolytes is critical. (42) Careful presurgical patient selection is the key to success because the risk of neural injury is higher with ETV than with shunt placement. Unnecessary ETV surgeries must, therefore, be avoided when possible.

OUTCOME

Variations in the temporal and spatial progression of hydrocephalus have relevant clinical consequences. A slow progression of ventriculomegaly over months allows the brain to respond with intrinsic repair mechanisms via cellular plasticity. Preferential expansion of the lateral ventricle's occipital horn can affect optic radiations and result in selective visual deficits without directly affecting motor function. (43)

Untreated neonatal hydrocephalus can be lethal, but with appropriate intervention, patients can survive well into adulthood with minimal complications. However, many shunts will fail over time. Shunt failure may be aseptic and involve obstruction, over- or underdrainage, or occult reasons for malfunction. It can also be related to infection, requiring removal of the entire shunt system and then replacement after appropriate antibiotic treatment. Long-term follow-up has shown shunt infection and obstruction rates as high as 16% and 79%, respectively. (44) When a shunt malfunctions due to obstruction, and revision is required, approximately 40% of patients will have event-free survival at 10 years.

Long-term studies have shown that individuals with shunt placement in childhood require approximately 2 to 4 revisions by the time they reach the third decade of life. (44)(45)(46) Unfortunately, the absence of shunt failure does not always equate to shunt independence because malfunction has been reported to occur up to 20 years after the initial shunt insertion. (46) The durability of the shunt tubing has not been studied well, but when discontinuity or kinking occurs along the shunt tract, shunt failure can result. If a patient ultimately becomes shunt independent, the shunt is not removed given that calcification and scarring along the tubing can increase surgical morbidity with removal. There is also a risk of damaging the highly vascular choroid plexus that may be scarred around or in close proximity to the proximal catheter.

Shunt placement can be complicated by over- or underdrainage. If a programmable valve was used at the time of shunt placement, the valve settings may be changed via noninvasive techniques to either increase or decrease CSF flow through the shunt as needed. However, in the case of nonprogrammable valves, an additional surgery is required to exchange the shunt valves. In neonatal hydrocephalus, overdrainage can result in slit ventricle syndrome and early suture closure (craniosynostosis). Valve regulation has reduced the incidence of over- and underdrainage, but both are important sequelae that must be monitored in the postoperative period. (47)

Shunt infections are often a result of skin flora, and stringent aseptic techniques must be used at the time of surgery to minimize and eliminate postoperative infection risk. Depending on the definition and duration of follow-up, infection has been reported to range from 0.2% to 8% per surgery. (48)(49) Risk factors of shunt infection are young age at the time of initial surgery, prematurity, IVH, and open neural tube defects as etiologic factors in hydrocephalus. (46)

Social integration and overall psychosocial well-being in patients with permanent CSF diversion relies largely on the underlying causes of neonatal hydrocephalus. (46) However, for preterm infants, ventriculomegaly remains one of the strongest predictors of impaired neurodevelopmental outcome. (50)

EVIDENCE SUMMARY

1. Neonatal, and pediatric hydrocephalus more broadly, is a complex disorder and there is no consensus on its appropriate treatment. A 10-part systematic review of the literature and guidelines was published in 2014 by the *Pediatric Hydrocephalus Systematic Review and Evidence-Based Guidelines Task Force.*
2. For PHH in the preterm neonate (23):
   - There is level 1 evidence (high clinical certainty) to recommend against the use of thrombolytic agents and diuretics.
   - There is level 2 evidence (moderate clinical certainty) suggesting that ventriculosubgaleal shunts reduce the need for daily CSF aspiration compared with VADs. There is level 2 evidence (moderate clinical certainty) to recommend against the use of serial LP to reduce the need for shunt placement or to avoid the progression of hydrocephalus.
   - There is level 3 evidence (insufficient) to recommend the use of ETV. In addition, there is insufficient evidence to recommend a specific weight or CSF parameters to direct timing of shunt placement.
   - Recently, there has been a movement to formally standardize the timing of temporary and permanent CSF diversion using an infant's weight, ventricle size, and other specific clinical parameters. Supportive data to help develop these guidelines are being generated.
3. Although fetal hydrocephalus is increasingly detected on routine antenatal surveillance, there are no guidelines to support clinical practice related to serial imaging, parental counseling, or mode and timing (fetal vs neonatal) of surgical intervention. Owing to the complexities involved, treating clinicians may wish to consider consultation with and referral to centers with expertise in fetal diagnosis and surgical intervention.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the ocular signs associated with increased intracranial pressure.
- Know the familial/genetic features of neurologic disorders associated with increased head circumference.
- Know the etiology, familial/genetic features, and abnormalities associated with hydrocephalus.
- Know the management and outcome of such management in an infant with hydrocephalus.
- Know the significance and management of mild ventriculomegaly detected on a prenatal ultrasound examination.

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American Academy of Pediatrics
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Index of Suspicion in the Nursery

1 Scrotal Swelling in a Term Infant

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AUTHOR DISCLOSURE Drs Alallah, Sulaiman, and Khattab have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male infant is born at 39 weeks' gestation via vacuum-assisted vaginal delivery due to fetal deceleration to a 37-year-old gravida 3, para 2 woman. The woman's pregnancy had been uncomplicated. Antenatal ultrasonography findings had been normal. The infant's birthweight is 3,755 g. The newborn was given a vitamin K injection at the time of birth. He is sent to the normal nursery with his mother in good condition; at 8 hours after birth, the mother notes that the infant has right scrotal swelling. He is transferred to the NICU for further evaluation and treatment.

The infant is stable on room air, with a temperature of 36.8°C, heart rate of 150 beats/min, respiratory rate of 55 breaths/min, and oxygen saturation of 94%.

On physical examination, he has no pallor and displays no irritability. The examination shows no evidence of skin bleeding or stigmata of congenital infection. There is no significant organomegaly on abdominal examination, and the rest of the systemic examination findings are within normal limits. Nontender bilateral scrotal swelling is noted to be more pronounced on the right (Fig 1), the swelling did not transilluminate, and the left testis is palpable. No bruising is seen on the groin initially. Abdominal examination findings are normal. There is no evidence of trauma.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute scrotal swelling in newborn includes the following:

- Testicular torsion
- Hydrocele
- Inguinal hernia
- Adrenal hemorrhage
- Birth trauma
- Scrotal hematoma

CASE PROGRESSION

On admission to the newborn nursery, an acute scrotum is initially suspected. Urgent scrotal ultrasonography showed both testes to be normal in their positions, sizes, and outline. A right scrotal fluid collection with minimal free hydrocele was seen with high-level echoes on scrotal ultrasound. No solid or cystic focal lesions were noted, and there was no evidence of testicular torsion. The abdominal ultrasonography findings were normal. Pediatric surgery was consulted, and the patient received conservative management.

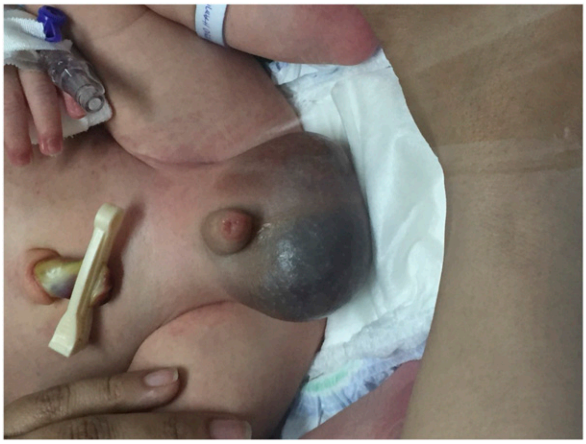

Figure 1. Infant with bilateral scrotal hematoma, which is more pronounced on the right, 2 days after birth.

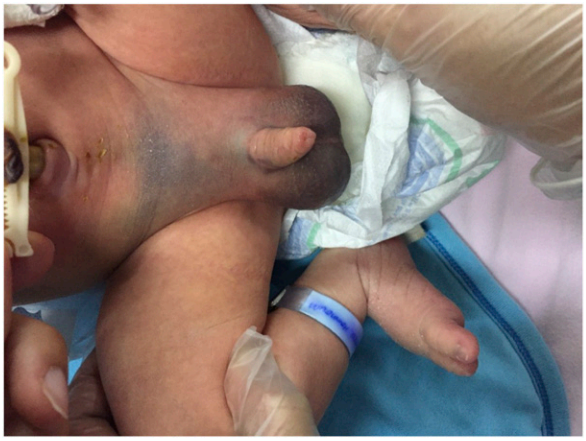

Figure 2. An extension of right scrotal hematoma in the right inguinal area, 3 days after birth.

Complete blood cell counts were as follows: platelets, 45×10³/μL (45×10⁹/L); hemoglobin, 13.5 g/dL (135 g/L), white blood cells, 15,000/μL (15×10⁹/L); hematocrit, 38%; and C-reactive protein, 1.5 mg/L (14.3 nmol/L). A platelet transfusion (10 mL/kg) was given. The platelet count after 1 hour was 30×10³/μL (30×10⁹/L), with a blood film of severe thrombocytopenia, hemoglobin of 10 g/dL (100 g/L), hematocrit of 28.4%, and white blood cell count of 13,000/μL (13.9×10⁹/L). A second transfusion of platelets (10 mL/kg) was given and repeat platelet count after 1 hour was 129×10³/μL (129×10⁹/L). Coagulation profile showed a prothrombin time of 15.8 seconds (normal 10–14 seconds), international normalized ratio of 1.4 (normal 0.01–1.24), and activated partial thromboplastin time of 41.2 seconds (normal 24–41 seconds). The infant was given nothing by mouth and only intravenous (IV) fluids. Partial evaluation for sepsis was performed, and IV antibiotic treatment with ampicillin and gentamycin was started. Transcranial ultrasonography of the brain had normal findings. Screening for *t*oxoplasmosis, *o*ther agents, *r*ubella (also known as German measles), *c*ytomegalovirus, and *h*erpes simplex was negative.

Pediatric hematology was consulted and IV immunoglobulin (1 g/kg) was given on 2 consecutive days for possible neonatal alloimmune thrombocytopenia (NAIT). On day 3 after birth, bluish discoloration was more prominent in the right inguinal area (Fig 2), so a repeat ultrasonography with renal Doppler was performed of the abdomen and pelvis, with normal findings and no evidence of adrenal hemorrhage. Daily complete blood cell count showed improving thrombocytopenia range (86→79→105→111×10⁹/L).

The infant remained stable with no evidence of active bleeding. Blood culture was negative. After completing a 5-day course of antibiotics, he was discharged on the sixth day after birth in stable condition with a platelet count of 111×10³/μL (111×10⁹/L) and improvement in the scrotal hematoma (Fig 3). A follow-up appointment was scheduled with hematology on discharge.

A follow-up visit 48 hours after discharge showed normal platelet count of 147×10³/μL (147×10⁹/L), with significant improvement in scrotal swelling. One week later, his platelet count was 495×10³/μL (495×10⁹/L), and in the third week a follow-up visit to the clinic showed complete resolution of the swelling (Fig 4).

ACTUAL DIAGNOSIS

The patient was diagnosed as having scrotal hematoma secondary to NAIT.

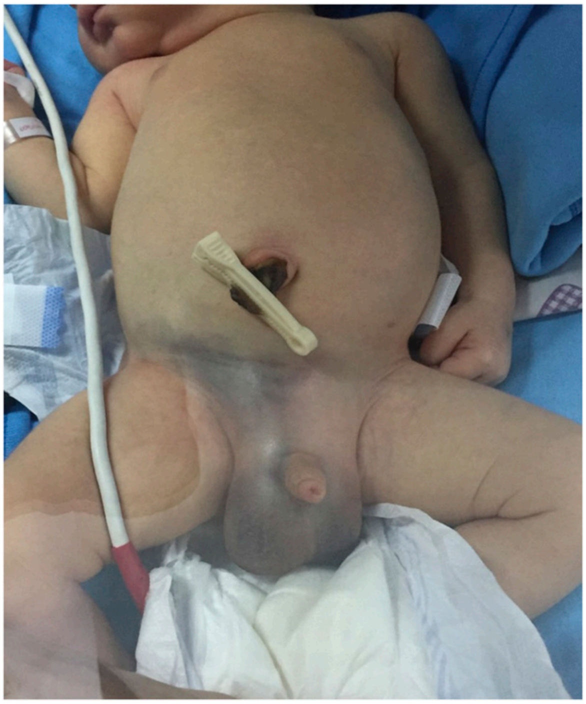

Figure 3. Just before discharge from the NICU, 6 days after birth.

DISCUSSION

Acute scrotal hematoma in the neonatal period is a rare condition that requires prompt diagnosis and possible urgent intervention. It commonly results from testicular torsion, adrenal hemorrhage, and birth trauma. (1) A few other cases of neonatal scrotal hematoma have been documented in the literature including spontaneous idiopathic hemorrhage of the scrotum. (2)

Our patient presented with acute scrotal swelling, which was thought to be testicular torsion and was excluded on scrotal ultrasonography. The swelling did not transilluminate as would be expected in the case of congenital hydrocele. There was no clinical feature suggestive of trauma. Abdominal ultrasonography excluded the adrenal hemorrhage as a cause of hemoscrotum.

Thrombocytopenia is defined as a platelet count less than $150\times10^3/\mu L$ ($150\times10^9/L$); severe neonatal thrombocytopenia occurs when the platelet count is less than $50\times10^3/\mu L$ ($50\times10^9/L$) and has been associated with significant bleeding such as intracranial hemorrhage. (3)

NAIT is the most common cause of thrombocytopenia in a full-term infant and resolves within 1 week. (4) This is attributed to immune-mediated destruction of fetal and neonatal platelets, and was seen in our case. The unusual presentation of our case was that of isolated scrotal hematoma with no petechial rash or other significant bleeding on screening ultrasonography. We treated our case with platelet transfusions and IV immunoglobulin because his platelet count was less than $50\times10^3/\mu L$ ($50\times10^9/L$) with a significant scrotal hematoma.

The ideal treatment for a neonate with NAIT is to provide HPA-1a-negative and 5b-negative platelets from the blood bank. But it was not available so random donor platelets were given, which was effective. Maternal platelets can only be used if they are washed because circulating antibodies will also be present.

It is important to consider a broad differential diagnosis in cases of acute scrotal hematoma including thrombocytopenia in the absence of other bleeding site or skin manifestation.

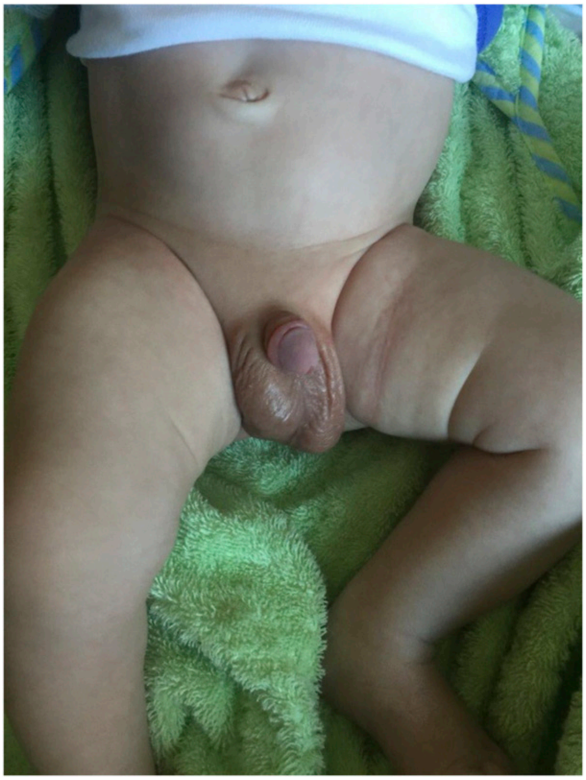

Figure 4. Clinic visit 4 weeks after birth.

Lessons for the Clinician

- Acute scrotal hematoma in the neonatal period is a rare condition that requires prompt diagnosis and possible urgent intervention.
- Scrotal hematoma most commonly occurs because of testicular torsion, adrenal hemorrhage, birth trauma or thrombocytopenia.
- Neonatal alloimmune thrombocytopenia is the most common cause of thrombocytopenia in a full-term infant and may be a cause of scrotal hematoma.

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- Know the clinical and laboratory manifestations and management of neonatal thrombocytopenia and thrombocytosis.

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2

Acute Respiratory Distress, Hypoxia, and Pulmonary Hypertension in the Nursery

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AUTHOR DISCLOSURE Drs Muise and Tran have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant is born at 39 weeks' gestation to a 28-year-old, gravida 3, para 2 woman who received regular prenatal care. Her history is significant for blood type O negativity (for which she received Rho(D) immunoglobulin at 28 weeks), hypothyroidism (treated with levothyroxine), polycystic ovarian syndrome (treated with metformin), and anxiety. The neonate is born via repeat cesarean section with vacuum assistance. The infant's Apgar scores are 9 and 9 at 1 and 5 minutes, respectively.

In the well-child nursery, the infant is hypoxic and has an oxygen saturation of 40%, requiring nasal continuous positive airway pressure of 5 cm H_2O and fraction of inspired oxygen (FiO_2) of 50%; she is transferred to the NICU.

FURTHER DIAGNOSTIC EVALUATION

In the NICU, she was noted to have increased work of breathing, and required nasal intermittent mandatory ventilation and FiO_2 of 50%. Chest radiography suggested respiratory distress syndrome versus pneumonia. Blood and urine samples were obtained for culture, and she was started on empirical antibiotic treatment for clinical pneumonia in the setting of presumed sepsis. Pediatric cardiology was consulted because of the clinical suggestion of pulmonary hypertension. Hyperoxia test, electrocardiography, and echocardiography showed no evidence of congenital heart disease. An incidental finding of ductus arteriosus thrombus extending to the main pulmonary artery and left pulmonary artery was uncovered on echocardiography (Figs 1 and 2).

Hematology consultation led to a recommendation of a complete thrombophilia evaluation including protein C, protein S, antithrombin III, homocysteine, and antiphospholipid antibody panel, all of which were normal. The initial platelet count was 152,000/μL (152×10^9/L), and there were no signs of consumptive coagulopathy. All laboratory values were within normal limits. The infant was given a bolus (75 U/kg) of unfractionated heparin and started on a high-dose heparin infusion (28 U/kg per hour); she subsequently made a transition to low-molecular-weight heparin after head ultrasonography demonstrated no intracranial hemorrhage.

Within the first week after birth, the infant was weaned off respiratory support and was stable in room air. Blood and urine cultures yielded no growth after 48 hours, and she completed a 7-day course of ampicillin and gentamicin for clinical pneumonia. She was also found to have ABO incompatibility; maternal blood

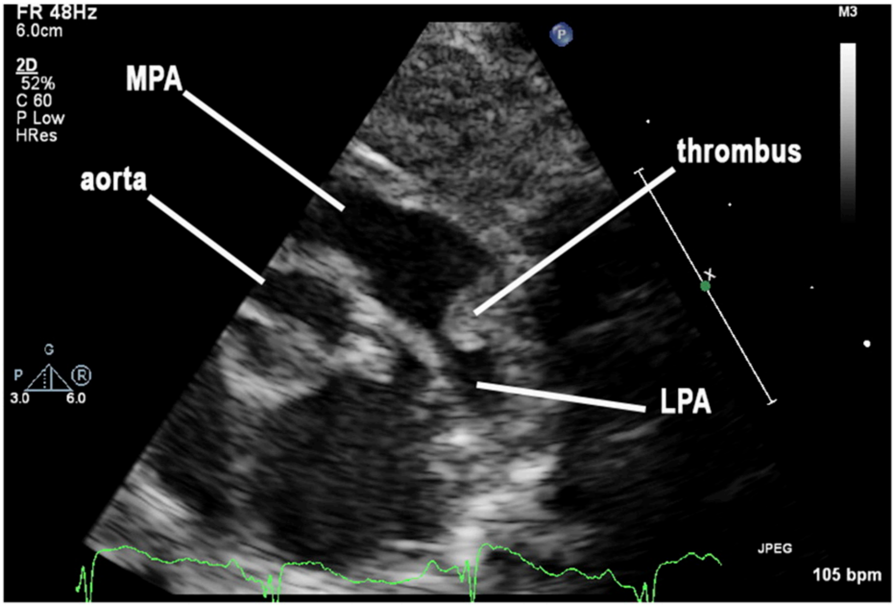

Figure 1. Echocardiographic parasternal short-axis view shows a cross-sectional image of the heart. Here the thrombus is protruding from the patent ductus arteriosus into the main pulmonary artery (MPA) and left pulmonary artery (LPA).

type was O negative, and the mother received Rho (D) immunoglobulin at 28 weeks' gestation; infant blood type was A positive with positive direct Coombs test result at birth, and the infant was treated with a 4-day course of phototherapy (her peak bilirubin level was 9.6 mg/dL [164.2 μmol/L]). Thyroid levels, obtained at discharge because of maternal hypothyroidism with unknown etiology, were within normal limits for age.

At outpatient follow-up, the infant was asymptomatic and without respiratory distress or feeding difficulty. Follow-up echocardiography performed at 1 month of age demonstrated normal Doppler profile in right, left, and main pulmonary arteries with no evidence of thrombus. Anticoagulation was stopped at 2 months of age, and repeat echocardiography identified no evidence of thrombus at 1 and 2 years of age.

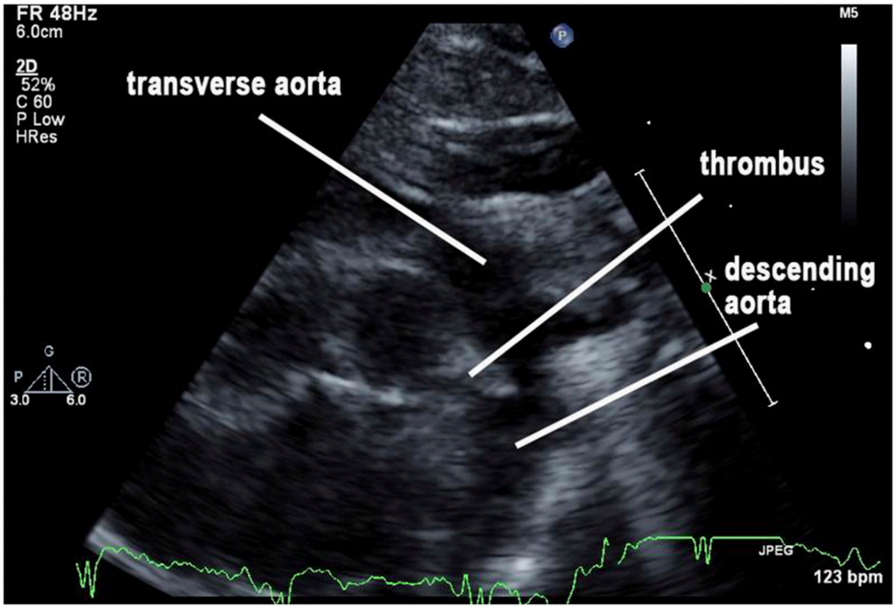

Figure 2. Echocardiographic images captured along the suprasternal notch view demonstrate the aortic arch. Here the patent ductus arteriosus thrombus is seen protruding into the descending aorta.

DISCUSSION

Thrombosis of the ductus arteriosus in the neonatal period is a rare finding, and has been historically associated with spontaneous ductus arteriosus aneurysm and with arterial access catheters. (1) Though typically asymptomatic, extension of ductus arteriosus thrombosis into other vessels or embolism can be life threatening, and may prompt surgical evaluation for possible thrombectomy and closure of the ductus. Medical management with either anticoagulation or antiplatelet therapy may also be considered in conjunction with or as an alternative to surgical correction.

At birth, the ductus arteriosus averages 15 mm in length and 44 mm in diameter. (2) It is derived from the embryologic portion of the left sixth aortic arch where it connects to the left main pulmonary artery, and is destined to become the ligamentum arteriosum. Physiologic closure of the ductus occurs in the hours to days after birth, and is a function of the contraction of the muscularis layer of the wall, causing infolding and buckling of the intima, beginning at the pulmonary artery end. Progression of physiologic closure leads to anatomic closure within several months. Thrombosis does not occur as a normal part of ductus arteriosus closure.

The incidence of ductus arteriosus aneurysm is low—1.5% detected on fetal echocardiography and 8.3% on postnatal echocardiography. (3) The theory most cited suggests that the aneurysm is formed by delayed closure of the aortic end of the ductus. (4) However, because some have been found as early as the third trimester, the mechanism of formation for prenatal compared with postnatal ductus arteriosus aneurysm may be different. The proposed mechanism for in utero aneurysm formation identifies higher flows through the ductus, suggesting that the aortic end is always open due to higher pressures. (4) Conical shape narrowing toward the pulmonary artery insertion creates a relative outflow obstruction across a ductus arteriosus aneurysm, and likely predisposes to thrombus formation. Serious complications of ductus arteriosus aneurysm are rupture, erosion, infection, and thromboembolism.

The neonatal period is a relative prothrombotic state, intensified by dehydration and acutely worsened in the settings of sepsis and trauma. Introduction of umbilical catheters also is associated with a predisposition to clot formation.

The Condition

Early reports of ductus arteriosus thrombosis largely described autopsy findings of dilated ductus arteriosus and thrombus. In 1972, Niwayama and Vadakan reported 13 historic cases and 3 new cases of thromboembolism due to anatomic anomalies (aneurysmal dilation, partial thrombosis without embolization, and mycotic vegetations). (2) Knowlson and Marsden reported 3 new cases of systemic thrombi originating in the ductus arteriosus diagnosed at autopsy. (5) Morisot et al reported a case of neonatal hypertension resulting from renal artery embolism caused by ductus arteriosus thrombosis, which was successfully treated with thrombolytic therapy. (6) Thrombosis of the ductus arteriosus with extension of the clot into the pulmonary artery, as in this case, has previously been described; however, anticoagulation failed to prevent the propagation of the thrombus and the neonate required surgical thrombectomy. (7) Maisel and Brenner published a case of spontaneous closure of a ductus arteriosus thrombosis in the setting of a prenatally diagnosed ductal aneurysm. (8)

More recent case reports include systemic thromboembolism, causing acute cerebral infarct diagnosed with computed tomography angiography, with the incidental finding of ductus arteriosus aneurysm. (3)

Treatment

Treatment of thrombus originating in the ductus arteriosus varies with the severity of cardiopulmonary compromise. Observation, systemic anticoagulation, and surgical thrombectomy have all been described as treatment modalities for ductus arteriosus thrombus. The objective of treatment is to prevent both propagation of existing thrombus and development of new thrombosis. Surveillance with serial echocardiography is also recommended. (7) A full hypercoagulable evaluation may be performed regardless of treatment to uncover common causes of a thrombophilic state.

CONCLUSIONS

This case describes a potentially fatal ductus arteriosus thrombus that presented within the first hours after birth with pronounced hypoxia. Incidental echocardiographic finding of ductus arteriosus thrombosis extending into the main pulmonary artery and left pulmonary artery identified the likely source of pulmonary hypertension causing respiratory distress. Thrombosis prompted a negative hypercoagulability evaluation and led to successful treatment with systemic anticoagulation and subsequent clinical improvement.

Lessons for the Clinician

- A term neonate presenting with hypoxia within hours of birth requires a rapid assessment and consideration of a broad differential diagnosis, which may include transient tachypnea of the newborn, ductal-dependent cardiac lesions, hypoglycemia, and early-onset sepsis.

- With concurrent history and physical examination, emergent respiratory support to ensure adequate ventilation and oxygenation is essential.
- Early echocardiographic examination to evaluate for cardiac causes of hypoxia and timely intervention should be considered.

ACKNOWLEDGMENTS

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American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the clinical features and differential diagnosis of persistent pulmonary hypertension.

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3 Ambiguous Genitalia in a Newborn

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AUTHOR DISCLOSURE Drs Viehl, Gaut, Dandamudi, and Davis have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 3,250-g term infant is born via cesarean delivery to a gravida 1, para 0 woman at a community hospital. There are no complications during pregnancy. All maternal serologic test results are negative, including indirect Coombs, rubella, rapid plasma reagin, hepatitis B surface antigen, human immunodeficiency virus, *Gonorrhea*, *Chlamydia*, and group B *Streptococcus*. The infant is delivered via cesarean section because of a failure to progress during induction of labor. Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. Growth parameters for weight, length, and orbitofrontal circumference are within the expected range for gestational age. Physical examination is notable for ambiguous genitalia with an enlarged clitoris with prepuce, enlarged labia majora bilaterally, and small labia minora bilaterally. No testicles are palpated within the inguinal canal. The infant is transferred to the NICU.

Abdominal and pelvic ultrasonography reveals normal-appearing adrenal glands, a normal-appearing uterus, and an absence of intra-abdominal gonads. A congenital adrenal hyperplasia (CAH) panel reveals normal levels of androstenedione, cortisol, dehydroepiandrosterone serum, deoxycorticosterone, 17-hydroxypregnenolone, 17-hydroxyprogesterone, testosterone, and 11-deoxycortisol. It reveals a markedly elevated level of progesterone of 261 ng/dL (830 nmol/L; normal range for our laboratory is <10 ng/dL [32 nmol/L] for a patient of this age). Chromosome analysis using fluorescence in situ hybridization reveals a 46,XY karyotype and a normal chromosomal microarray. Antimüllerian hormone level is in the normal range for a genotypic male. The infant is discharged from the NICU with a recommendation to follow up with the endocrinologist.

The infant presents to the hospital at 4 months of age with concerns for several metabolic derangements, including serum sodium of 115 mEq/L (115 mmol/L), potassium of 6.9 mEq/L (6.9 mmol/L), bicarbonate of 14 mEq/L (14 mmol/L), urea nitrogen of 65 mg/dL (23 mmol/L), creatinine of 2.9 mg/dL (256 μmol/L), and calcium of 7.0 mg/dL (1.75 mmol/L). Dipstick urinalysis shows pH 7.0, 3+ protein, 3+ blood, with trace leukocyte esterase and no nitrites. The urine has more than 600 mg/dL of protein and 38 mg/dL of creatinine. Kidney ultrasonography reveals large echogenic kidneys. The left kidney measures 7.64 cm (3.3 standard deviations above the mean) and the right kidney measures 7.34 cm (2.9 standard deviations above the mean). Further genetic testing and input from consulting services confirm the diagnosis.

DISCUSSION

Differential Diagnosis

An infant with virilization always raises concerns for CAH. An elevation of 17-hydroxyprogesterone would be suggestive of 21-hydroxylase deficiency, the most common cause of CAH. In the setting of the XY karyotype with the appearance of female external genitalia (enlarged clitoris and labia majora), undervirilization may be responsible. Forms of CAH that need to be considered are 17α-hydroxylase and 3β-hyroxysteroid dehydrogenase deficiencies as well as lipoid hyperplasia and P450 oxidoreductase deficiency. However, an isolated elevation in progesterone does not necessarily suggest any particular diagnosis, especially given recent gestation. Antimüllerian hormone in the normal range helps rule out the diagnosis of müllerian duct abnormalities. Other diagnostic possibilities in cases of ambiguous genitalia and/or differences/disorders of sexual development include androgen insensitivity, 5α-reductase deficiency, Leydig cell hypoplasia, aromatase deficiency, Smith-Lemli-Opitz syndrome, and gonadal dysgenesis.

The concomitant kidney involvement (nephrotic range proteinuria and elevated serum creatinine) in a genotypic male with undervirilization is concerning for a genetic renal syndrome such as a diagnosis on the Denys-Drash syndrome (DDS)–Frasier syndrome spectrum, WAGR (Wilms tumor, anirida, genitourinary anomalies, and intellectual disability [formerly referred to as mental retardation]) syndrome, or other *WT1* mutations (Table). Next-generation sequencing was performed on this patient to evaluate 34 genes implicated in genetic causes of steroid-resistant nephrotic syndrome. Testing revealed a pathogenic heterozygous missense variant, p.H445R (also known as p.H377R), in exon 8 of *WT1*, supporting the diagnosis of DDS in this patient. (1)(2) No significant variants were identified in any of the 33 additional genes tested.

The Condition

DDS is a congenital/infantile nephrotic syndrome caused by genetic mutations on exons 8 and 9 of the *WT1* gene. Patients have a male karyotype (46,XY), gonadal dysgenesis (external genitalia are ambiguous or appear as completely female—also known as male pseudohermaphroditism), and nephrotic syndrome and/or kidney failure (usually within the first 3 years of life). There is a greater than 70% predisposition for the development of Wilms tumor. There is also a predisposition for developing gonadoblastoma in the dysmorphic (streaked) gonads.

DDS is an autosomal dominant disorder. However, most mutations occur de novo. All mutations, recorded to date, result in a premature stop codon. The WT1 protein is a transcriptional regulator of genes necessary for normal kidney development and ongoing function. The gene consists of 10 exons, with exons 7 to 10 encoding 4 zinc finger transcription factors that regulate gene expression by DNA and RNA binding. (3)

Although DDS can present with focal segmental glomerulosclerosis on kidney biopsy, most often, it shows diffuse mesangial sclerosis (DMS) (Fig 1A). DMS is characterized by immature-appearing glomeruli with increased mesangial matrix and hyperplastic visceral epithelial cells. As the lesions progress, the glomerular tuft becomes more retracted with capillary loop obliteration and increasing mesangial matrix. DMS is not specific for DDS and also has been identified in patients with pathogenic genetic variants in *PLC1E* and *LAMB2*. (4) The risk for gonadoblastoma is almost exclusively in the XY karyotype, and occurs because of neoplastic transformation of germ cells of the dysgenetic gonads. The risk for gonadoblastoma in DDS is approximately 4%.

Clinical Management

The presentation of significant kidney dysfunction requiring emergent kidney replacement therapy, large echogenic kidneys, streaked gonads, and a pathogenic heterozygous missense variant, p.H445R in *WT1*, prompted us to recommend proceeding with prophylactic bilateral nephrectomy and gonadectomy. Pathologic examination of the kidneys reveals diffuse mesangial sclerosis and scattered intralobar nephrogenic rests (Figs 1A and 1B). Nephrogenic rests are precursors of Wilms tumor.

Gonads have pathology consistent with fallopian tubes, seminiferous tubules and epididymis. Within the seminiferous tubules there are abnormal foci of Sertoli cells consistent with pregonadoblastoma lesions. After healing from the intra-abdominal surgery, the infant was discharged from the hospital on peritoneal dialysis. The parents have decided to raise her as a girl. Performing prophylactic bilateral nephrectomies and gonadectomy before the development of Wilms tumor or gonadoblastoma will allow proceeding to kidney transplantation when medically stable.

Lessons for the Clinician

- Denys-Drash syndrome (DDS) presents with the triad of early-onset nephropathy, genotypic male with undervirilization, and predisposition to Wilms tumor.
- *WT1* mutations that cluster in exons 8 and 9 are responsible for DDS.

TABLE. Wilms Tumor 1 Gene Mutations and Associated Syndromes

SYNDROME/DISEASE ASSOCIATED WITH *WT1* GENE MUTATION	SITE OF MUTATION IN THE *WT1* GENE ON CHROMOSOME 11P13	CLINICAL PHENOTYPE	TUMOR RISK
Denys-Drash syndrome	Mutations at either exon 8 or 9	Karyotype 46,XY*:	70%–90% risk of developing Wilms tumor; greater incidence of bilateral disease
		Undervirilization with ambiguous or normal-appearing external female genitalia Streaked gonads/gonadal dysgenesis (male pseudohermaphroditism) Infant-onset, steroid-resistant, nephrotic syndrome with progression to ESKD by 3 years of age	4% gonadoblastoma
Frasier syndrome	Mutations in intron 9 altering the ratio of WT1 isoforms	Karyotype 46,XY:	4% risk of developing Wilms tumor
		Complete undervirilization; normal-appearing external female genitalia Streaked gonads/gonadal dysgenesis; (male pseudohermaphroditism) Diagnosis often identified during evaluation for primary amenorrhea Late childhood/adolescent onset, steroid-resistant, nephrotic syndrome with progression to ESKD by 20 years of age	40% risk of gonadoblastoma
WAGR syndrome	Large deletion of adjacent genes at the p13 chromosomal region including *PAX6* gene; *PAX6* is responsible for aniridia and intellectual impairment	Karyotype 46,XY or XX Aniridia Ambiguous genitalia/malformations; Gonadal dysgenesis Intellectual disability CKD and/or proteinuria	45%–60% risk of developing Wilms tumor
WAGRO syndrome	Large deletion in chromosomal region extending beyond p13 to include deletion of *BDNF* gene on 11p14	Karyotype 46,XY or XX Features of WAGR syndrome along with childhood obesity and pancreatitis	45%–60% risk of developing Wilms tumor
Isolated nephrotic syndrome (excludes syndromic forms listed before)	Most common mutations are located at either exon 8 or 9. Many of the same mutations have been identified in patients with Denys-Drash	Karyotype 46,XY or XX Steroid-resistant nephrotic syndrome with diffuse mesangial sclerosis and/or FSGS *WT1* mutation identified in 2%–3% of all cases of isolated nephrotic syndrome not associated with developing Wilms tumor If accounting for all *WT1* mutations in steroid-resistant nephrotic syndrome then a mutation is identified 6%–8% of the time	N/A
Meacham syndrome	Mutations at either exon 8 or 9	Karyotype 46,XY: Undervirilization; abnormal internal female genitalia often double vagina Complex cyanotic heart lesions Hypoplastic left heart Hypoplastic lungs; diaphragmatic hernia/abnormalities	No reports of Wilms tumor, likely due to death in early infant/early childhood

Continued

TABLE. **(Continued)**

SYNDROME/DISEASE ASSOCIATED WITH *WT1* GENE MUTATION	**SITE OF MUTATION IN THE *WT1* GENE ON CHROMOSOME 11P13**	**CLINICAL PHENOTYPE**	**TUMOR RISK**
Wilms tumor	About 20% of patients with Wilms tumor have a *WT1* gene mutation	Karyotype 46,XY or XX Most common kidney cancer in the pediatric population Overall, 5th most common pediatric cancer 80% present with abdominal mass Overall, about 10% of Wilms tumor occurrences are associated with a syndrome (see above and below)	N/A
Syndrome/disease associated with increased risk of Wilms tumor, but not with *WT1* gene mutation	Site of mutation	Clinical phenotype	Tumor risk
Beckwith-Wiedemann syndrome	Mutation or epigenetic change at 11p15 region	Polyhydramnios Macroglossia Macrosomia Hemihyperplasia Omphalocele Anterior ear lobe crease Pits on the helix of the ear/linear ear fissures Neonatal hypoglycemia	20%–30% risk of developing Wilms tumor
Isolated hemi-hypertrophy syndrome	No causative mutation identified	1 side or 1 area of the body larger than the other	6% risk of developing Wilms tumor
Perlman syndrome	Mutation at 2q37 in *DIS3L2*	Macrosomia Deep-set eyes Kidney hamartomas	30% risk of developing Wilms tumor
Simpson-Golabi-Behmel syndrome	Mutation at Xq26 in *glypican-3*	Bulldoglike facies Polydactyly Heart disease	8% risk of developing Wilms tumor
Faconi anemia	Biallelic mutations at 13q12-13 in the *BRCA2* gene	Microcephaly Short stature Hypoplastic/absent thumbs Café au lait lesions Hypogenitalia Cytopenia	20% risk of developing Wilms tumor
Sotos syndrome	Mutation at 5q35 in *NSD1* gene	Macrocephaly Macrosomia Large hands and feet Premature teeth eruption Poor coordination Variable intellectual ability	2%–3% risk of Wilms tumor

CKD=chronic kidney disease; ESKD=end-stage kidney disease; FSGS=focal segmental glomerulosclerosis; N/A=not applicable; WAGR=Wilms tumor, aniridia, genitourinary malformation, intellectual disability (formerly mental retardation); WAGRO=WAGR syndrome with childhood-onset obesity.
**XX karyotype has been reported, not generally associated with abnormal gonadal development, and therefore has a low risk for gonadoblastoma. However, the risk for Wilms tumor development is thought to remain high and on par with the XY karyotype.*

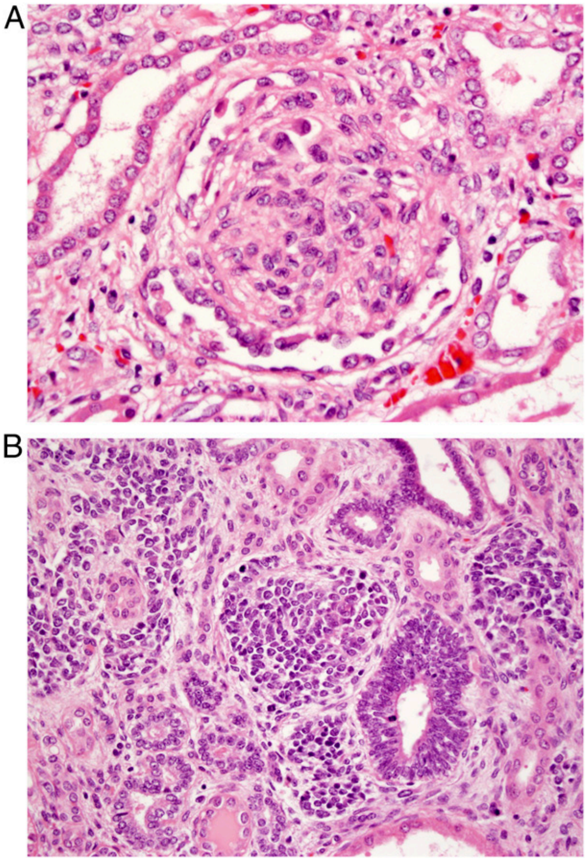

Figure. A. Representative glomerulus in a patient with a heterozygous missense variant, p.H445R in *WT1*, showing diffuse mesangial sclerosis (hematoxylin and eosin [H&E], ×600). B. Representative interstitial region from the same patient with Denys-Drash syndrome demonstrating an intralobar nephrogenic rest, a precursor of Wilms tumor (H&E, ×400).

- The same *WT1* mutation in one patient can present with a different phenotype or syndrome in another patient (Table).
- Genotypic females (XX) with mutations associated with DDS have a high risk of developing Wilms tumor, but are not thought to be at risk of developing gonadoblastoma.
- In DDS, prophylactic nephrectomy and gonadectomy should be performed to prevent the development of Wilms tumor or gonadoblastoma. The timing of the procedure remains controversial, but most would recommend performing before age 3 years.
- In differences of sex development, including ambiguous genitalia, the decision to raise the child as a boy or girl is best with family cooperation, a specialized multidisciplinary team, and ongoing psychological considerations.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the etiology of abnormal sexual differentiation.

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Case 3: Ambiguous Genitalia in a Newborn

Luke Viehl, Joseph P. Gaut, Raja Dandamudi and T. Keefe Davis

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Fluctuant Mass on an Infant's Scalp

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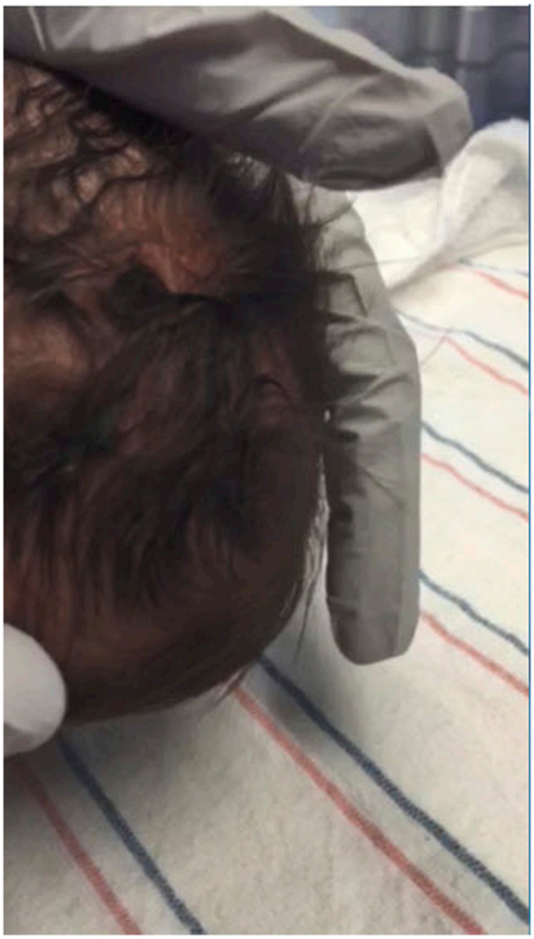

Video. Click here to view the video.

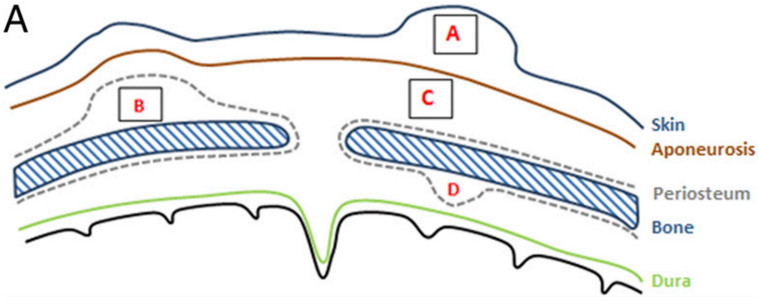

Figure 1A. Locations for potential collections that are exterior and interior to an infant's skull.

AUTHOR DISCLOSURE Drs Whitesel and Brodsky have disclosed no financial relationships relevant to this article. Dr Brodsky is the current editor-in-chief of *NeoReviews*. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

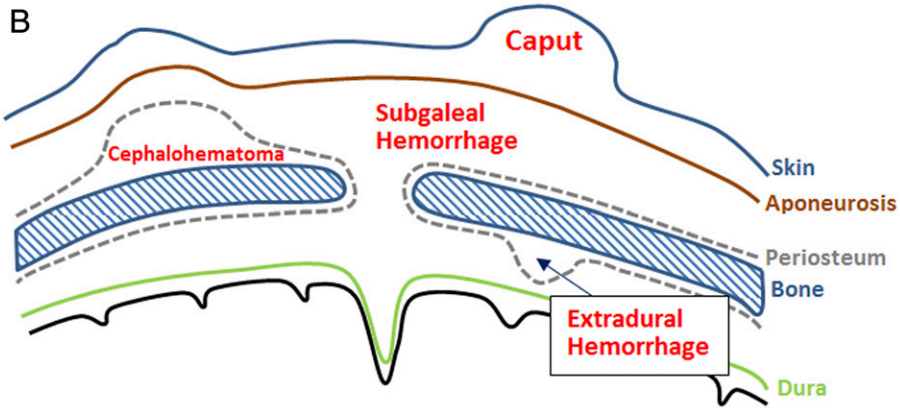

Figure 1B. Locations of caput, cephalohematoma, subgaleal hemorrhage, and extradural hemorrhage.

CASE

A term infant has the following scalp examination [click on the video].

VIDEO

Of the options shown in Fig 1A (A, B, C, or D) of the top of an infant's head, what is the most likely location of the involved area in this infant?

CRITIQUE

The video of this newborn shows a moderate-to-large fluctuant mass gathered in the dependent portion of the neonate's scalp. Upon gentle tapping of the boggy collection, there is a clearly visible fluid wave. This finding is most consistent with a subgaleal hemorrhage.

Subgaleal hemorrhage is a serious, potentially fatal event in a newborn. It is caused by the rupture of large, bridging, emissary veins that connect the scalp veins to the intracranial dural sinuses. When these veins rupture, blood accumulates between the periosteum and the galeal aponeurotica, a large potential space composed of loose connective tissue. This space extends without restriction across the cranium and can hold as much as 260 mL of blood. (1) (Note: The average total blood volume in a term infant is 80–90 mL/kg.) A hemorrhage of 20% to 40% of a newborn's total circulating blood volume into the subgaleal space is sufficient to lead to hypovolemic shock, disseminated intravascular coagulation, and death. Figure 1B denotes the location of a subgaleal hemorrhage as well as other extracranial findings.

Subgaleal hemorrhages are rare events. The incidence has been estimated to occur more commonly in vacuum-assisted deliveries (59 of 10,000) compared with spontaneous vaginal deliveries (4 of 10,000). (2)(3) In addition to being strongly associated with vacuum-assisted vaginal deliveries, other risk factors include primigravida status of the mother, malposition of the fetal head, difficult extraction, macrosomia, prolonged second stage of labor, forceps delivery, prematurity, cephalopelvic disproportion, and male sex. (1)(4)

An affected infant presents with a diffuse swelling of the scalp that obscures suture lines and is fluctuant on palpation. This swelling may be present at delivery or may not become apparent until several hours or, less commonly, up to several days after delivery. The fluid can shift when the head is repositioned and can accumulate at the nape of the neck or behind the ears, displacing the ears inferiorly. The head circumference of affected infants can increase; even small increases in the head circumference (eg, 1 cm) may account for as much as 40 mL of blood because of the large potential space for the hemorrhage. (3)(4)(5)

If the subgaleal hemorrhage is small, the infant may be asymptomatic and the hemorrhage can resolve over time without need for intervention. However, an infant with a severe subgaleal hemorrhage may present with severe anemia and hypovolemic shock (ie, poor perfusion, severe metabolic acidosis). Because symptoms may progress over time, an infant with a suspected subgaleal hemorrhage requires ongoing monitoring of vital signs, as well as serial hematocrit and occipital frontal circumference (OFC) measurements. (3) If the hematocrit is decreasing, coagulation studies should be performed and bilirubin levels monitored. The classic presentation of a significant hemorrhage includes tachycardia, a falling hematocrit (Note: the hematocrit may be normal initially), and increasing OFC in the first 24 to 48 hours. (3)(6)(7) Though subgaleal hemorrhage is a clinical diagnosis, it can also be viewed radiographically, with ultrasonography (Fig 2). Associated complications include intracranial hemorrhages (subarachnoid, intraventricular, or intraparenchymal) and skull fracture. (1)

For an infant with a severe subgaleal hemorrhage, management focuses on early and aggressive volume resuscitation with packed red blood cells and normal saline, correction of the coagulopathy, and management of shock.

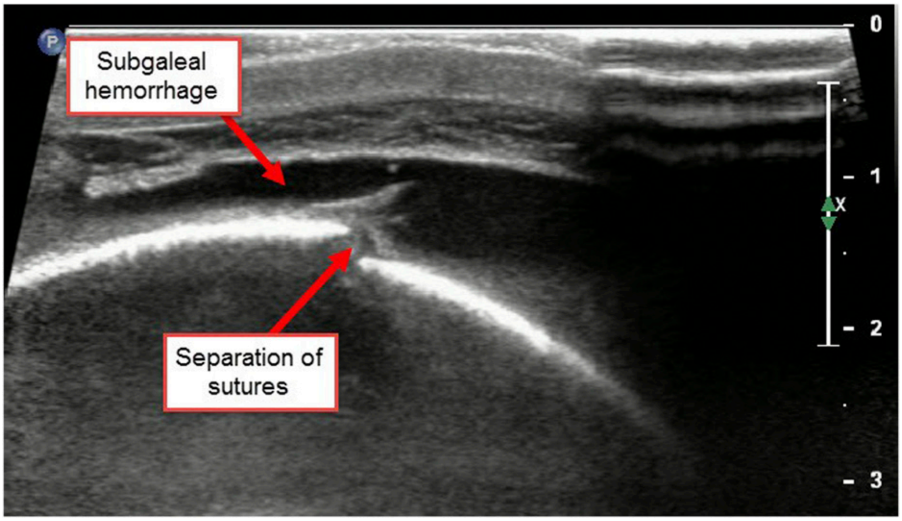

Figure 2. Ultrasonographic image showing subgaleal hemorrhage.

Early recognition and aggressive treatment are critical for a good outcome, and mortality rates have been reported to be anywhere from 2.7% up to 22.8%, depending on the severity of the hemorrhage. (1)(2)(3)

Differentiating subgaleal hemorrhages from other extracranial pathologies such as cephalohematomas and caput succedaneums is important, because prompt recognition and treatment in the setting of a severe subgaleal hemorrhage are critical.

Cephalohematomas result from the rupture of vessels beneath the periosteum, and therefore, unlike subgaleal hemorrhages, are restricted by the periosteal attachments. Found in 1% to 2% of deliveries, cephalohematomas present typically as a unilateral, firm swelling that does not cross the suture line. The bleeding is slow; therefore, the swelling can be delayed for several hours to days. These rarely cause significant blood loss, and will typically resolve by 3 to 4 weeks without any intervention. Potential complications include indirect hyperbilirubinemia and infection. Occasionally, an area of calcification may develop, creating a palpable subcutaneous nodule that reabsorbs over the following 3 to 4 months. (3)(6)(7)

A caput succedaneum, on the other hand, is very common after vaginal delivery, and occurs as a result of the increased pressure on the infant's head by the uterus and vaginal wall during labor. This pressure causes hemorrhagic edema between the scalp and subcutaneous tissue, but above the periosteum. The clinical presentation is one of a soft, superficial collection that crosses suture lines. There can be overlying erythema, petechiae, and ecchymosis. This collection is largest at the time of birth and typically resolves within 48 to 72 hours. (3)(6)(7) Because blood loss with a caput succedaneum is minimal, no intervention is required.

Correct Response

C, subgaleal hemorrhage. A represents a caput, B represents a cephalohematoma, and D represents a subdural hemorrhage.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the diagnostic, clinical, and imaging features of extracranial hemorrhage, including cephalohematoma and subgaleal hemorrhage.

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A Catastrophic Fetal Intracranial Hemorrhage

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal values for arterial umbilical cord gas values and indications of acidosis are defined in the Table.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

AUTHOR DISCLOSURE Drs Clear, Braginsky, and Plunkett have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. **Arterial Umbilical Cord Gas Values**

	pH	Pco_2 (mm Hg)	Po_2 (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤–10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤–10
Metabolic acidosis	<7.20	<60	Variable	≥–10
Mixed acidosis	<7.20	>60	Variable	≥–10

**Normal ranges from* Obstet Gynecol Clin North Am. *1999;26:695.*

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

  Absent: Amplitude range is undetectable
  Minimal: Amplitude range is greater than undetectable to 5 beats/min
  Moderate: Amplitude range is 6–25 beats/min
  Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation.

  Examples of these tracings include any of the following:

  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - Recurrent late decelerations
    - Recurrent variable decelerations
    - Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol*. 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

A 29-year-old gravida 2, para 1-0-0-1 woman presents to the labor and delivery department at 30 2/7 weeks' gestation with decreased fetal movements. She had noted decreased fetal movement 5 days earlier and had a nonstress test the previous day (ie, 30 1/7 weeks' gestation) that became reactive after almost 2 hours of monitoring and many attempts at fetal stimulation. She received no other evaluation at that time. She otherwise had no complaints, and denied any contractions, vaginal bleeding, or leaking of fluid.

The patient's obstetric history included a full-term vaginal delivery complicated by preeclampsia with severe features. The current pregnancy was complicated only by a recent maternal diagnosis of avascular necrosis of the femoral head. She had no other medical concerns. Her gynecologic history included an abnormal Pap smear with positive high-risk human papillomavirus. Her family history was notable for her brother who had a recent diagnosis of an "autoimmune clotting disorder" treated with clopidogrel and warfarin; the patient reported that her brother was doing well and had no other information regarding his diagnosis

The patient's initial evaluation revealed that she had stable vital signs. The initial FHR tracing is shown in Fig 1.

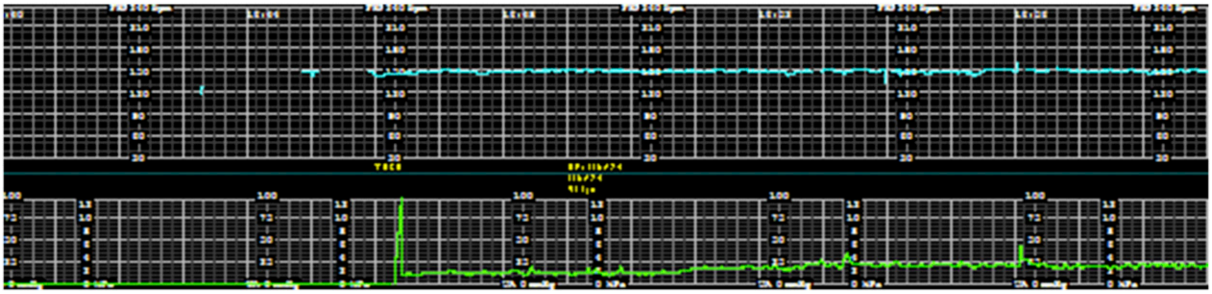


Figure 1. Electronic fetal monitoring strip 1.

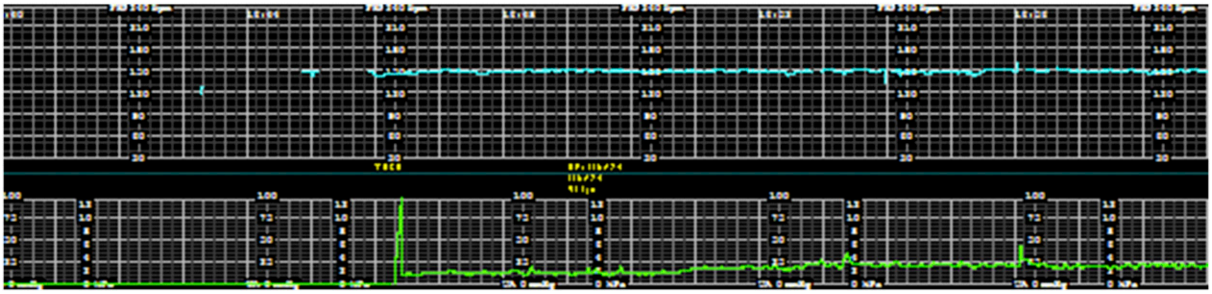


Figure 1. Electronic fetal monitoring strip 1.

Findings on EFM strip 1 are as follows:

- Variability: Minimal
- Baseline rate: 160 beats/min
- Uterine contractions: None
- Interpretation: Category II in the setting of minimal variability
- Differential diagnosis: Placental insufficiency, fetal hypoxemia, sleep cycle
- Action: Ultrasonography performed

Given the patient's complaint of decreased fetal movement and a category II FHR tracing, bedside ultrasonography was performed. The fetal brain was grossly abnormal with an area of increased echogenicity concerning for bleeding versus intracranial mass. No fetal movement was visualized, and the biophysical profile was 2/8 for a normal amniotic fluid volume. Because the FHR tracing remained at category II, the obstetric team decided to perform comprehensive ultrasonography and fetal brain magnetic resonance imaging (MRI) the following morning. The obstetric team consulted the neonatologist, who met with the patient and her family about the potential diagnoses and possible outcomes associated with each diagnosis.

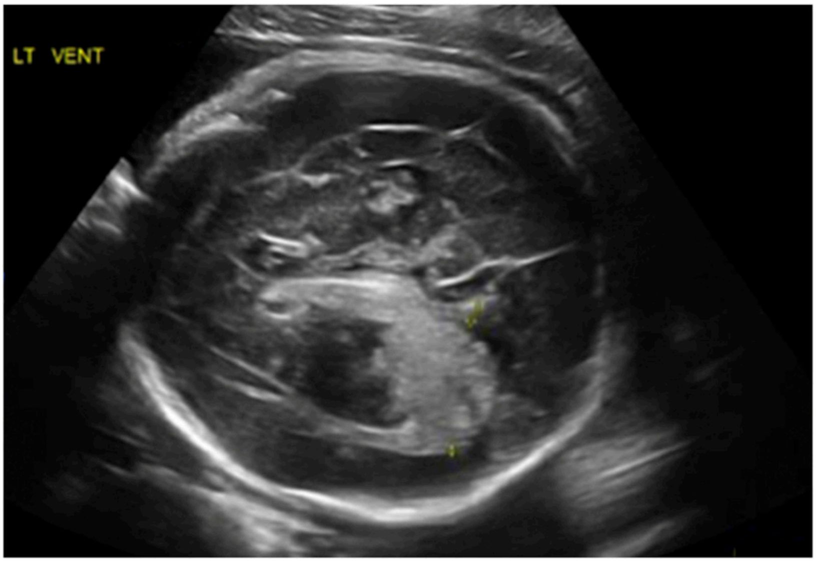


Figure 2. Transverse section of the fetal brain at the level of the lateral ventricle showing hyperechoic area of intraventricular hemorrhage.

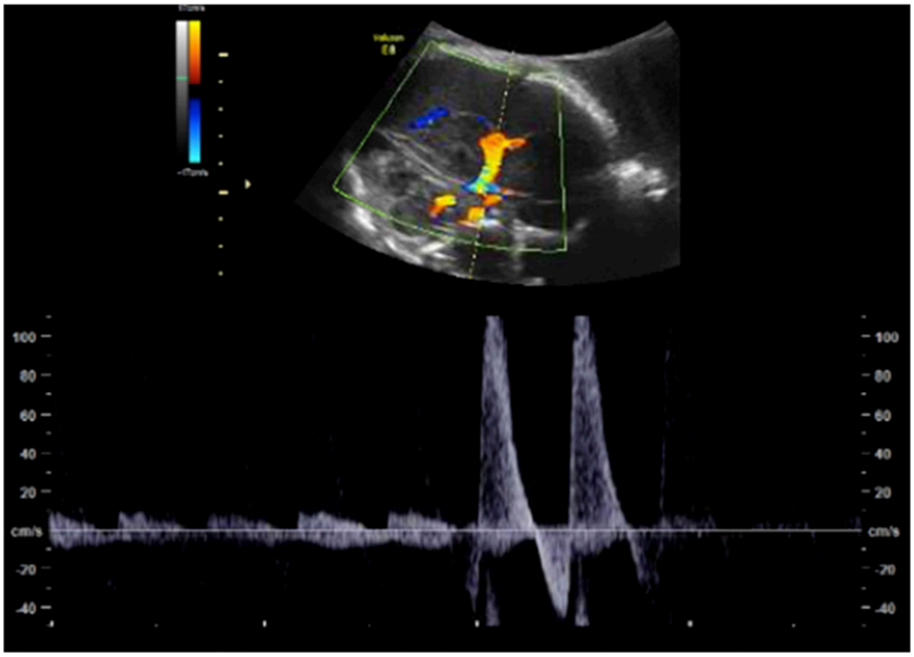
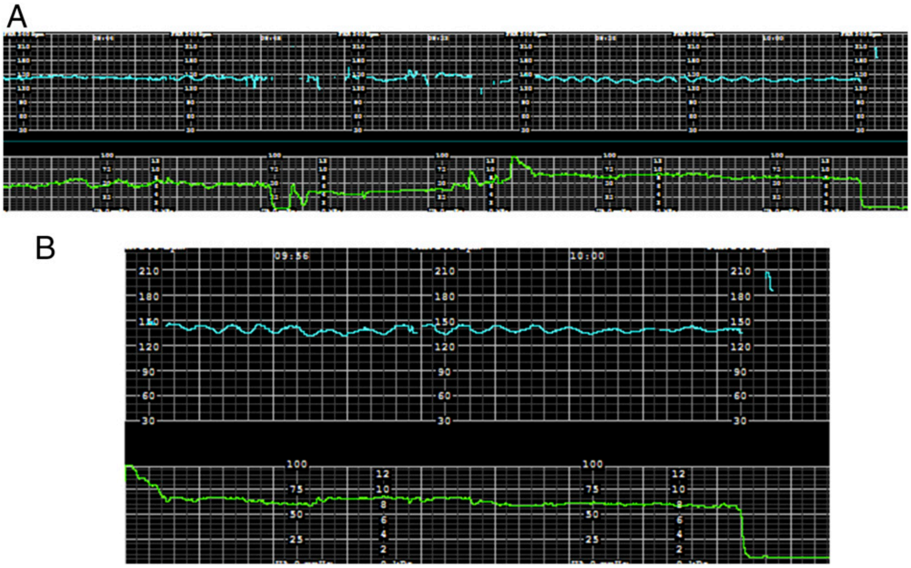


Figure 3. Fetal middle cerebral artery Doppler assessment demonstrating elevation above 1.5 multiples of the median.

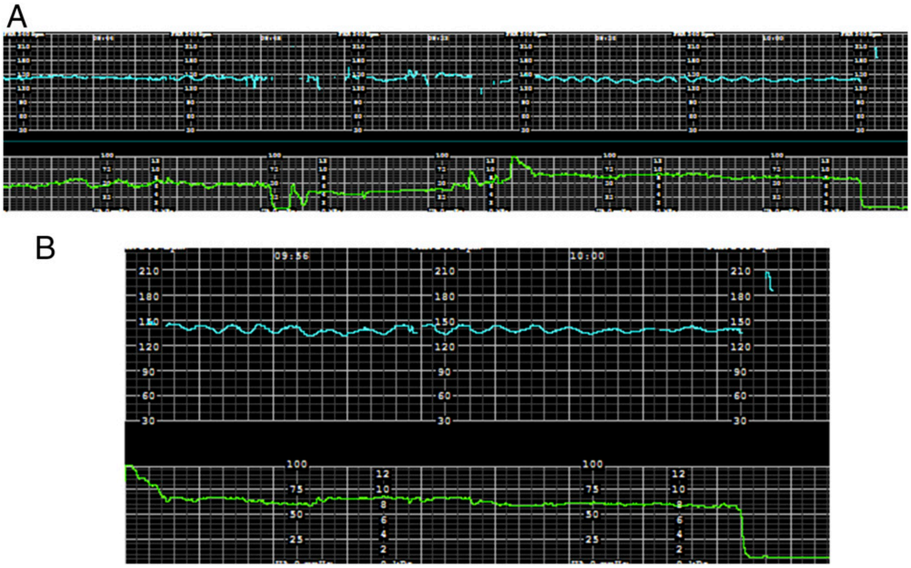
In the morning, the patient underwent a comprehensive ultrasound evaluation. Bilateral intracranial intraventricular echogenic areas were noted, which appeared larger than the previous day. The fetal middle cerebral artery (MCA) Doppler findings were elevated above 1.5 multiples of the median, indicating moderate to severe fetal anemia. These findings were consistent with a diagnosis of bilateral intraventricular hemorrhages.

The ultrasound scans of the fetal brain and MCA Doppler images are shown in Figs 2 and 3, respectively.

The patient was transferred back to labor and delivery and a repeat FHR tracing was obtained (Fig 4a). Figure 4b shows a larger image of the last 7 minutes of this tracing.



Figures 4a and 4b. Electronic fetal monitoring strip 3.



Figures 4a and 4b. Electronic fetal monitoring strip 3.

Findings on EFM strip 3 are as follows:

- Variability: Absent
- Baseline rate: 140 beats/min
- Episodic pattern: Sinusoidal
- Uterine contractions: None
- Interpretation: Category III
- Differential diagnosis: Fetal anemia, fetal hypoxemia
- Action: Urgent primary cesarean delivery

A sinusoidal heart rate tracing is a category III tracing and, as such, requires urgent action. It is characterized by its sinusoidal appearance and smooth contours with lack of variability. It is a sign of severe fetal anemia. Because of the concern about worsening fetal status, the obstetric team performed an urgent primary cesarean delivery. The surgery was uncomplicated, with the delivery of a female infant weighing 2,570 g. Neonatology was present at the delivery, and the infant's Apgar scores were 6, 8, and 8 at 1, 5, and 10 minutes, respectively. The infant appeared extremely pale and required intubation immediately after delivery because of apnea. She was given a blood transfusion in the operating room via an umbilical line for a hematocrit of 9%. She was transferred to the special care nursery in stable condition. The infant's coagulation studies were abnormal, with elevated prothrombin and partial thromboplastin times, increased international normalized ratio, and a decreased fibrinogen level, but her platelet counts were normal. Brain ultrasonography 2 days after birth showed a marked amount of complex extra-axial fluid and moderate ventriculomegaly, as well as an abnormal appearance of the gyri and sulci with cystic encephalomalacia of the left parietal lobe, hemorrhagic ischemic changes in the left parietal, occipital, and temporal lobes (Figs 5 and 6).

The neonatology team evaluated the infant for an infection with blood and cerebrospinal fluid testing, results of which were negative for cytomegalovirus (CMV), parvovirus, and herpes simplex virus. A fetal MRI revealed large bilateral hemispheric parenchymal hemorrhages within the parietal, occipital, and posterior temporal lobes; large intraventricular hemorrhages; and bilateral multiseptated subdural hemorrhages over the entire cerebral hemisphere and posterior superior cerebellum (Fig 7).

The infant underwent successful extubation and is currently undergoing continued hematologic evaluation and monitoring in the special care nursery.

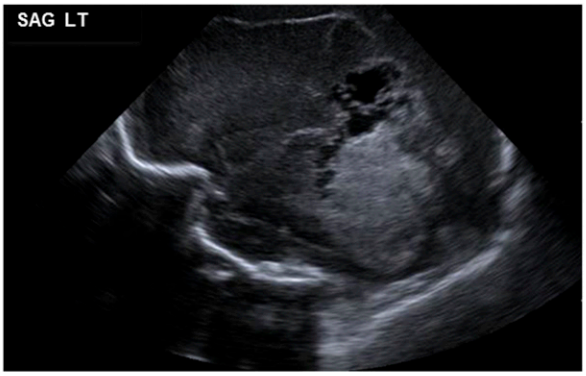


Figure 5. Head ultrasound scan on day 2 of postnatal life.

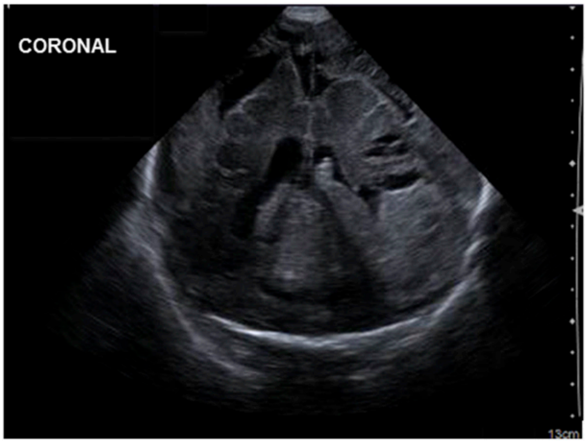


Figure 6. Head ultrasound scan on day 3 of postnatal life.

DISCUSSION

Fetal Intracranial Hemorrhage

In utero fetal intracranial hemorrhage is very rare, with an incidence of 1 to 2 in 100,000. The most common type of intrauterine cerebral hemorrhage is intraventricular, but bleeding can occur in other locations, such as the cerebellum, subdural, or subarachnoid space, or within the cerebral parenchyma. (1) Cerebral hemorrhages can occur because of trauma, fetal coagulopathy, alloimmune thrombocytopenia, infection, vascular malformation, tumor, hypoxic-ischemic stroke, and certain gene mutations with a predisposition to hemorrhage. (2) Most cases of fetal intracranial hemorrhage occur in the early third trimester because of the immaturity of the germinal matrix and its susceptibility to changes in cerebral blood flow. (3) Typically, in utero intracranial hemorrhages are classified in grades, with increasingly poor prognoses accompanying the higher grades of hemorrhage. (2)

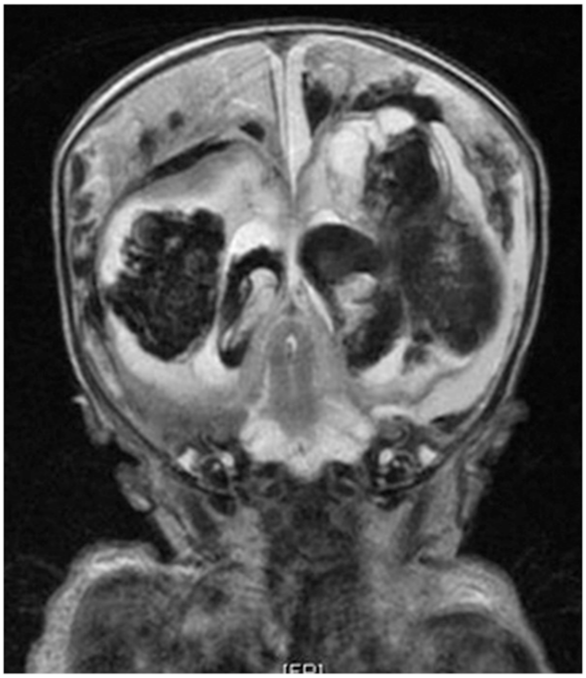


Figure 7. Neonatal brain magnetic resonance imaging scan.

- Grade I is isolated to the germinal matrix at the caudothalamic groove.
- Grade II is an intraventricular hemorrhage without ventricular dilation.
- Grade III involves ventricular dilation.
- Grade IV includes periventricular hemorrhagic infarction. (2)

These grades can be determined with ultrasonography. (1)

Ultrasound Findings and Differential Diagnosis of Fetal Intracranial Hemorrhage

Antenatally diagnosed fetal intracranial hemorrhage is most commonly detected in the late second or third trimesters of pregnancy. (2)(4) The ultrasonographic appearance of fetal intracranial hemorrhage varies depending on the type, location, severity, and chronicity. (5) Intracranial hemorrhage initially appears as an echogenic collection in the fetal cranium, most often in the periventricular or intraventricular region because of bleeding from the germinal matrix. (5)(6)

As the hematoma liquefies, this asymmetric, echogenic mass eventually makes a transition to contain hypoechoic components. In the case of intraventricular hemorrhage, ventriculomegaly may be seen on ultrasonography and may also lead to destruction of the surrounding white matter, resulting in a porencephalic cyst. (5)(6)

There are several other causes for cerebral injury, which may lead to, and ultrasonographically mimic, fetal intracranial hemorrhage, including fetal hypoxic-ischemic stroke, intrauterine infection, and intracranial neoplasm. Similar to intracranial hemorrhage, the appearance of a fetal stroke is variable, though it initially appears as increased cerebral echogenicity. (5) The lesion may later progress to microcephaly, cystic intraparenchymal lesions, and cortical malformations. (5) Fetal infection, particularly CMV infection, may also mimic intracranial hemorrhage on ultrasonography. Specifically, CMV may appear as periventricular or intraparenchymal echogenicities, ventriculomegaly, or microcephaly. (5) In addition, CMV-induced parenchymal injury may lead to cystic degeneration of the periventricular white matter and the appearance of a septation in the posterior aspect of the lateral ventricle. (5)(6) Blood clots in the lateral ventricles may also be mistaken for choroid plexus cysts, because both conditions appear as echogenic areas in the ventricles. (6) Finally, fetal intracranial neoplasms need to be considered in the differential diagnosis of fetal intracranial hemorrhage. At least 1 case report has described congenital glioblastoma multiforme presenting with similar ultrasonographic features as fetal intracranial hemorrhage. (7)

Definition and Causes of Fetal Anemia

Fetal anemia is defined as a hemoglobin or hematocrit concentration that is more than 2 standard deviations below the mean for a given gestational age. (8) Fetal anemia can result from many possible underlying etiologies, all of which share a common final pathway of fetal hydrops in cases of severe anemia. In addition to fetal hemorrhage, other causes of fetal anemia include red blood cell alloimmunization, hemoglobinopathies, fetomaternal hemorrhage, inherited hemolytic disorders, congenital leukemia, infections, vascular tumors or arteriovenous malformations, and genetic conditions. Red cell alloimmunization is the most common cause of fetal anemia in the United States. (8)(9) α-Thalassemia, particularly if homozygous with absence of all 4 α-globulin chains, is also a common cause of fetal anemia and hydrops in patients of Asian or Mediterranean descent. (9) Fetomaternal hemorrhage is common and can lead to significant fetal anemia and hydrops. Inherited hemolytic disorders that may lead to fetal anemia include glucose-6-phosphate dehydrogenase deficiency, and erythrocyte enzyme deficiencies such as pyruvate kinase deficiency. (9) Fetuses with trisomy 21 are at increased risk for congenital leukemia secondary to abnormal myelopoiesis. (8) Fetal infections that may lead to anemia include parvovirus, toxoplasmosis, coxsackievirus, and syphilis. (8)(9) Vascular tumors or arteriovenous malformations may be present in either the fetus or the placenta and are a rare cause of fetal anemia. Genetic conditions associated with fetal anemia include Fanconi anemia and Diamond Blackfan anemia, as well as inherited metabolic disorders. (8)

Antenatally, fetal anemia can be detected based on elevated fetal MCA Doppler studies as well as a sinusoidal FHR pattern, both of which were seen in the present case. (4)(9) According to the NICHD, a sinusoidal FHR pattern is defined as a "visually apparent, smooth, sine-wave–like undulating pattern in FHR baseline with a cycle frequency of 3 to 5 per minute, which persists for 20 minutes or more." (10) The presence of a sinusoidal pattern requires immediate evaluation of fetal oxygenation and timely intervention, because it is associated with severe fetal acidemia. (9)

MCA Doppler to Assess for Anemia

Fetuses with anemia have elevated cardiac output and decreased blood viscosity. This combination, along with fetal shunting of blood to the cerebral vasculature, increases the velocity of blood flow through the MCA. (11) In 2000, Mari et al produced a landmark study demonstrating that peak systolic velocity (PSV) through the MCA is predictive of moderate to severe fetal anemia. Moderate fetal anemia was defined as less than 0.65 to 0.55 times the median of hemoglobin whereas severe was defined as less than 0.55 times the median hemoglobin value for gestational age. MCA PSV at 1.5 multiples of the median for gestational age demonstrated a 100% sensitivity (confidence interval of 86–100) for moderate to severe fetal anemia. (11)

MCA Doppler ultrasonography is a noninvasive technique that has virtually replaced amniocentesis in the evaluation of fetuses at risk for anemia. In the past, the bilirubin level in the amniotic fluid was used as a marker for hemolysis in fetuses at risk for hemolytic disease. (12) Bilirubin levels were assessed by the change in the optical density at the wavelength of 450 (Δ-OD450). Oepkes et al found MCA PSV studies to be superior in the detection of fetal anemia when directly compared with amniotic fluid Δ-OD450 measurement. (12) The higher accuracy and lower-risk profile have made MCA Doppler ultrasonography the test of choice to assess for fetal anemia.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the risk factors (including genetic abnormalities) for and evaluation and management of a fetus or infant with prenatal vascular brain injury.

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NeoReviews 2018;19;e493
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A Case of Neonatal Thrombocytopenia and Seizures: Diagnostic Value of Hyperpigmentation

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THE CASE

A male newborn presented to the emergency department of a rural hospital in South India at 3 days of age with poor feeding, excessive crying, and unsettled behavior. Over the next few days, he developed seizures, followed by increasing hyperpigmentation that is most pronounced over his face and neck.

Prenatal and Birth Histories

- Male infant born to a 24-year-old primigravida at 38 6/7 weeks' gestation via spontaneous vaginal delivery
- Pregnancy was complicated by polyhydramnios, premature rupture of membranes, and fever 1 day before delivery (highest documented temperature 101°F [38.3°C]; associated with chills, body aches, fatigue, transient macular rash)
- Intravenous antibiotics given to the infant's mother during the intrapartum and postpartum period
- Blood culture and investigations of the mother for endemic diseases Dengue fever and malaria, and urinary tract infection were negative
- Apgar scores 8 and 9 at 1 and 5 minutes, respectively
- Birthweight 2.98 kg

Presentation

The infant breastfed well during the first 48 hours but became ill on the third day after birth with poor feeding, excessive crying, and unsettled behavior. He was admitted to the NICU for further evaluation and management.

Vital Signs

- Temperature: 98.7°F (37.1°C)
- Respiratory rate: 45 breaths/min
- Oxygen saturation: 97% in room air
- Heart rate: 140 beats/min
- Capillary refill time: 2 seconds
- Peripheral pulse volume: normal

Physical Examination

- Head: Normal fontanelles and facies
- Skin: Mild icterus present; no rash or petechiae
- Lungs: Clear bilaterally; no signs of increased work of breathing
- Cardiovascular: Normal heart sounds and perfusion
- Abdomen: Soft to palpation; no organomegaly; umbilicus normal

AUTHOR DISCLOSURE Drs Reddy and Jinka have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

- Neurologic: Alert; normal tone; symmetrical limb movements; irritable; accepted oral feedings offered to settle him
- Skeletal: Limbs and spine normal

Laboratory Studies

The infant's blood test results on day 1 of admission (Table) showed severe thrombocytopenia (12,000/μL [12.0×10^9/L]), lymphopenia (10.3%), and abnormal coagulation studies (international normalized ratio 7, prothrombin time >300 seconds, and activated partial thromboplastin time >300 seconds).

PROGRESSION

The infant received platelet and fresh frozen plasma transfusions soon after admission to the NICU in view of the severe thrombocytopenia and coagulopathy, but he did not

TABLE. **Laboratory Results and Timing of Blood Product Transfusions**

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 8	DAY 12	DAY 17	NORMAL VALUES
Hemoglobin, g/dL (g/L)	17.5 (175)	18.5 (185)	14.8 (148)	14.6 (146)	14.4 (143)	13.2 (132)	12.1 (121)	12.7 (127)	11.6 (116)	14–21 (140-210)
WBC, $\times10^3$/μL ($\times10^9$/L)	9.4 (9.4)	9.7 (9.7)	12.8 (12.8)	13 (13)	11 (11)	12.8 (12.8)	12 (12)	9 (9)	7.2 (7.2)	6–21 (6–21)
Platelets, /μL ($\times10^9$/L)	12,000 (12)	19,000 (19)	20,000 (20)	41,000 (41)	30,000 (30)	14,000 (14)	15,000 (15)	37,000 (37)	135,000 (135)	150,000–450,000 (150–450)
INR	7		1.4		1.5		1.2			0.6–1.4
PT, s	>300	>200	17		17.5		14.2			10–15
aPTT, s	>300	>200	38.2		37		29.3			25–59
Total bilirubin, mg/dL (μmol/L)	10.8 (184)	9 (154)								As per Bhutani curve
Conjugated bilirubin, mg/dL (μmol/L)	0.8 (13.6)	0.1 (1.7)								<20% of total bilirubin
AST, IU/L (μkat/L)		154.5 (2.5)								26–98 (0.4–1.6)
ALT, IU/L (μkat/L)		20.7 (0.3)								6–40 (0.1–0.7)
ALP, IU/L (μkat/L)		116.4 (1.9)								100–360 (1.6–6.0)
Serum albumin, g/L		3.1 (31)								3.5–5 (35–50)
STP, g/dL (g/L)		4.9 (49)								6–8 (60–80)
CRP, mg/L (nmol/L)	18 (171.4)			5 (47.6)						<10 (95.2)
BUN, mg/dL (mmol/L)	20.6 (7.4)									2–20 (2.1–7.1)
Serum creatinine, mg/dL (μmol/L)	0.5 (44.2)									0.3–1.1 (27–100)
Serum sodium, mEq/L (mmol/L)	136 (136)									131–145 (131–145)
Serum potassium, mEq/L (mmol/L)	5 (5)									3.2–5.9 (3.2–5.9)
Serum chloride, mEq/L (mmol/L)	106 (106)									97–108 (97–108)
Blood culture	NG									
Platelet transfusion	+	+				+	+			
FFP transfusion	+	+								

Data are from admission days 1 to 17. ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; FFP=fresh frozen plasma; INR=international normalized ratio; NG=no growth; STP=serum total protein; WBC=white blood cell count.

show any bleeding manifestations at this stage. Thrombocytopenia persisted, along with deranged coagulation on day 2 of admission. Additional blood product transfusions were needed, as shown in the Table. On day 2 of admission, he developed episodes of desaturations and generalized tonic seizure activity. Head imaging and amplitude-integrated electroencephalography were not performed because the treating hospital did not have this capability. Recurrent seizures were managed with intravenous infusions of phenobarbital, levetiracetam, and midazolam and mechanical ventilation (Fig 1). No further seizures occurred after the midazolam infusion. Lumbar puncture was not performed in view of thrombocytopenia and coagulopathy. Midazolam and phenobarbital were discontinued after 3 days. Ventilation was weaned and the infant underwent extubation and began continuous positive airway pressure on day 6 of admission. Intravenous levetiracetam was changed to an oral form on day 6 and continued until discharge. On day 7 of admission, he showed spontaneous crying and activity. He developed mild generalized edema involving the face, trunk, and limbs during the first week of illness (which could have been due to capillary leak or multiple blood product transfusions).

His thrombocytopenia persisted for 2 weeks. Blood-stained gastric aspirates prompted administration of vitamin K (to manage coagulopathy, though the infant had received vitamin K soon after birth) and pantoprazole. During the course of his illness, blood glucose, blood pressure, skin perfusion, and urine output remained normal. Nasogastric tube feedings with breast milk were started on day 4 of admission and full feedings were achieved on day 8 of admission. He also received meropenem and cefotaxime in accordance with prevalent antibiotic sensitivity patterns in severe sepsis cases in the unit.

By day 7 of admission, he developed gradually increasing hyperpigmentation interspersed with areas of small, round, hypopigmented spots over his face and neck (Fig 2). This progressed to deep hyperpigmentation of his entire body with a unique appearance of pronounced pigmentation over his nose and perioral area over the next few days.

Differential Diagnosis

Bronze baby syndrome
Chikungunya
Dengue
Enterovirus, adenovirus, Epstein-Barr virus, herpes simplex virus
Familial glucocorticoid deficiency
Intracranial hemorrhage
Meningitis/encephalitis
Sepsis

ACTUAL DIAGNOSIS

Congenital Chikungunya

The appearance of intense hyperpigmentation was a unique feature of the illness that led to identifying the most likely cause of this presentation: congenital chikungunya infection. This infant's clinical course is also consistent with congenital chikungunya infection. (1)(2)(3) We could not obtain a laboratory diagnosis because of a lack of appropriate laboratory facilities at the treating hospital, but there is strong epidemiologic support for this diagnosis. According to the database from the National Vector Borne Disease Control Programme in India, 64,057 chikungunya

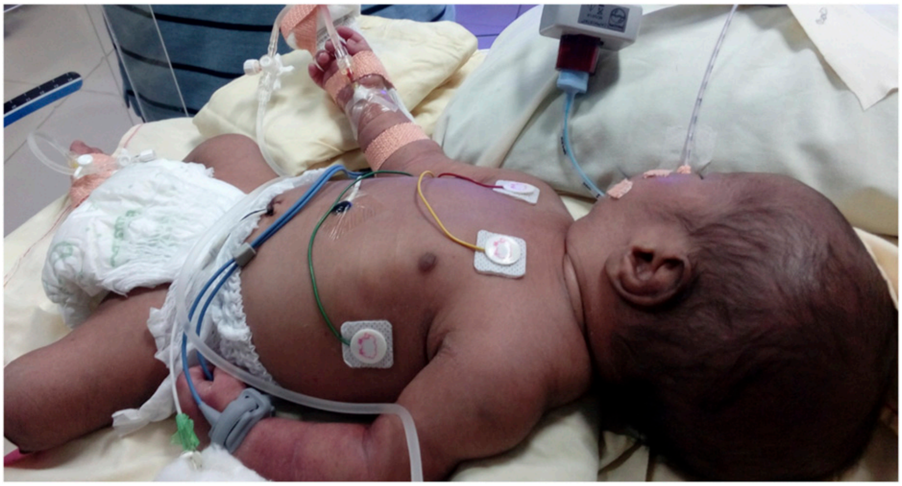

Figure 1. Appearance on day 3 of admission.

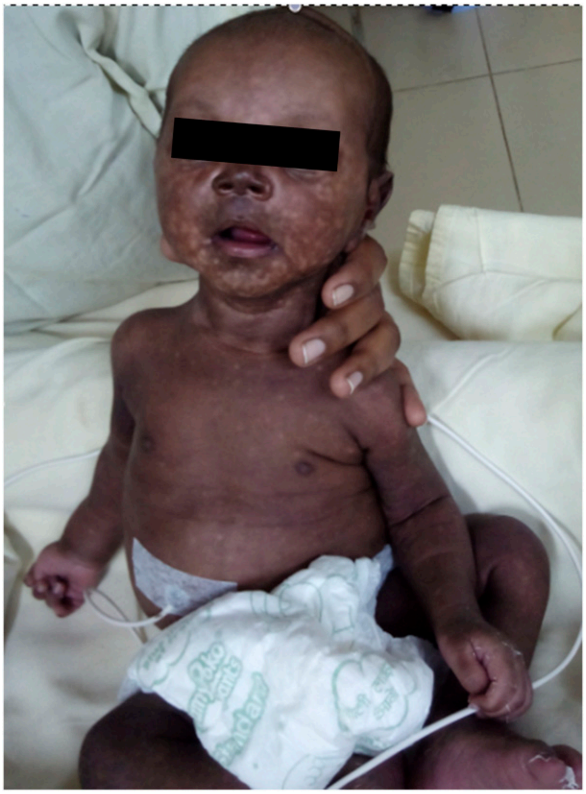
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Figure 2. Generalized hyperpigmentation with a distinctly prominent pigmentation of the patient's nose.

cases were reported in India during 2016 and 15,666 of these occurred in Karnataka state which is in close proximity to the location of this patient and his family.

Follow-up

Over the next 2 months, the infant's hyperpigmentation resolved gradually. Head ultrasonography at 3 weeks of age showed right frontal lobe cyst (5 mm) with normal appearance of rest of the visualized brain. At 3 and 6 months' follow-up, he was thriving. Neurologic examination did not show any abnormalities–he had normal and symmetric tone and power in all limbs with normal deep tendon reflexes. He attained normal developmental milestones.

WHAT THE EXPERTS SAY

Chikungunya is an arboviral disease transmitted by mosquito species *Aedes aegypti* and *Aedes albopictus*. It is endemic to South America, sub-Saharan Africa, Indian subcontinent, and Southeast Asia. Imported cases have occurred in Europe and North America. (4) Clinical features of infection in adults and children include an incubation period of 4 to 7 days, sudden onset of high fever and disabling joint and muscle pain, maculopapular rash, gastrointestinal symptoms, and less frequently, hemorrhagic symptoms such as petechiae, purpura, epistaxis, or bleeding gums. (5) Maternal-fetal transmission rate is approximately 50% during the intrapartum period. (4) The placental barrier is impermeable to chikungunya virus during the antepartum period. Vertical transmission does not occur in pregnant women infected more than 7 days before delivery. Transmission is believed to occur primarily through the transplacental route shortly before delivery due to contact of viremic maternal blood with placental barrier gaps during labor. (4) Consequently, infected newborns are asymptomatic at birth. (4) Delivery by cesarean section does not have a protective effect on viral transmission. (4)

Congenital chikungunya presents within 7 days after birth with the following signs and symptoms:

- Fever (79%)
- Pain (Neonatal Pain and Discomfort Scale score >6) (100%)
- Rash (82%)
  - o Various types have been reported, including rubelliform, rubeoliform rashes; bullous dermatitis; and erythroderma, followed by brownish hyperpigmentation (in dark-skinned infants, the degree of hyperpigmentation is more severe, as seen in this infant)
- Peripheral edema (58%)
- Thrombocytopenia (76%)
- Lymphopenia (47%)
- Prolonged prothrombin time (65%)
- Elevation of aspartate aminotransferase (77%)
- Seizures
- Coma (50%)
- Hemorrhagic syndrome
- Hemodynamic instability (5)

Skin manifestations in infants include a polymorphous rubellalike or roseolalike rash or erythroderma followed by desquamation of the extremities and brownish discoloration of the limbs and face, and in some cases, bullous dermatitis. (4)(5)(6) Infants presenting with encephalopathy show pathologic magnetic resonance imaging findings (cerebral edema and hemorrhages) that progress to developmental/neurologic abnormalities such as cerebral palsy, ataxia, and blindness. (4)(5) Laboratory diagnosis can be obtained with reverse transcriptase polymerase chain reaction (RT-PCR) during the first 5 days of illness or with immunoglobulin M–capture enzyme-linked immunosorbent assay after 5 to 7 days of illness. (4) Virus can be detected in the cerebrospinal fluid with RT-PCR but cerebrospinal fluid chemistry and cytology are usually normal. (5)

Congenital chikungunya should be considered in the differential diagnosis in newborns presenting with thrombocytopenia and encephalopathy in parts of the world where the virus is prevalent. Hyperpigmentation during the course of illness in an infant presenting with thrombocytopenia is diagnostic of chikungunya infection.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the differential diagnosis and syndromes associated with hyperpigmented lesions, including cafe au lait spots, giant hairy nevus, incontinentia pigmenti, and pigmented nevi.

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ANSWER KEY FOR AUGUST 2018 NEOREVIEWS

Neonatal Hypotonia: 1. B; 2. D; 3. C; 4. B; 5. A.

The Placenta and Neurodevelopment in Preterm Newborns: 1. A; 2. C; 3. E; 4. C; 5. B.

A Case of Neonatal Thrombocytopenia and Seizures: Diagnostic Value of Hyperpigmentation

Vudum Sridhar Reddy and Dasaratha Ramaiah Jinka

NeoReviews 2018;19;e502

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Answer Key appears on page e568.

Birth-Associated Neonatal Encephalopathy: Postresuscitation Care in West African Newborns

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Education Gaps

1. Clinicians caring for newborns in low-resource settings need to recognize that several local and complex dynamics influence the burden of perinatal asphyxia in West Africa.
2. Appropriate use of clinical scores/tools may improve diagnostic accuracy of birth-associated neonatal encephalopathy.
3. Therapeutic hypothermia without an effective package of intensive monitoring and care may not be safe.
4. Prevention, early diagnosis, and management of secondary causes of brain injury are critical for improving health outcomes.

Abstract

The West African subregion has the highest burden of neonatal mortality globally and the neonatal mortality rate is decreasing very slowly. A high proportion of newborn deaths are preventable and improved quality of care can reduce long-term morbidity in survivors. Perinatal asphyxia is the major cause of death and disability in term infants in the subregion. Neonatal resuscitation training programs have reduced stillbirths and early neonatal mortality but the overall effect on survival to discharge, population-based perinatal mortality, and long-term impairment is uncertain. Gaps in the health system and quality of postresuscitation care for affected newborns may defeat gains from global efforts to improve care around the time of birth. The aim of this review is to discuss the current situation of postresuscitation care of term infants with presumed birth-associated neonatal encephalopathy in West Africa. Limitations in diagnosing and treating affected infants and feasible interventions to improve acute and postdischarge care are discussed.

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ABBREVIATIONS

HBB	Helping Babies Breathe
NE	neonatal encephalopathy
NRT	neonatal resuscitation training
PA	perinatal asphyxia

Objectives After completing this article, readers should be able to:

1. Describe the burden and causes of birth-associated neonatal encephalopathy in West Africa.
2. Recognize limitations in diagnosis and appropriate management of neonatal encephalopathy in West Africa.
3. Review feasible community and facility-based interventions to reduce death and disability of newborns with encephalopathy in West Africa.

INTRODUCTION

The West African subregion is composed of 17 low- and low-middle income countries with an estimated 350 million people of great diversity in culture, language, religion, and colonial legacy (Fig). It has the highest burden of neonatal mortality globally. (1)(2) Available data on major causes of neonatal deaths and disability are estimates because about half of all births still occur at home without skilled providers, vital registration systems are relatively weak, and health systems face many challenges. (1)(3)(4) Efforts by countries to improve maternal-newborn health outcomes have resulted in a significant increase in facility-based antenatal and delivery services. (4) However, there are still major gaps in the quality of services provided around the time of birth, and preventable birth complications, especially perinatal asphyxia (PA), remain a major cause of death and disability. (5)(6)

Figure. United Nations subregions of Africa and West Africa. Printed with permission from the United Nations: West Africa, Map No. 4533, October 2014, United Nations (http://www.un.org/Depts/Cartographic/map/profile/westafrica.pdf).

PA occurs when there is interruption of blood flow and gas exchange to the fetus around the time of birth. Significant interruption results in hypoxic brain injury and neonatal encephalopathy (NE). The "golden minute"—the first minute after birth—provides a crucial window of opportunity for skilled essential care to reduce death and disability. (7) Standardized neonatal resuscitation training (NRT) programs such as Helping Babies Breathe (HBB) have significantly improved resuscitation skills of frontline providers and reduced deaths on the first day after birth. (8)(9)(10) Although HBB may reduce intrapartum-related neonatal mortality by 30% in low-resource settings, the overall effect of NRT on survival to discharge, population-based perinatal mortality, and long-term impairment is uncertain. (7)(11)(12) Improving the quality of care beyond the time around birth may save more lives and reduce severe disability.

In West Africa, many births still occur at the community and primary health facility level, often without a skilled provider or 1 skilled provider attending to both the mother and newborn. (4) Newborns who require assistance with breathing or have a weak or no cry at birth may not receive effective resuscitative care. However, with government investments in community-based health services, the HBB program is making inroads into intrapartum care at all levels of health service delivery. (13) Consequently, an increasing number of successfully resuscitated newborns are being referred to higher-level facilities for postresuscitation care. This review describes the situation in West Africa and suggests options that may reduce the burden of birth-associated NE and improve hospital-based postresuscitation care for affected term newborns.

THE BURDEN OF PA

The burden of PA reflects the quality of maternal-newborn health services; underlying factors for inadequate services in the subregion have been described. (3) In Africa, the West Africa subregion has the poorest indices for facility-based maternal care; about 50% of births still occur at home with 20% occurring with no person present and only 35% attended by a physician or nurse/midwife. (14) Inequalities in access to health care and wealth contribute significantly to giving birth with no one present, and Nigeria accounts for a significant proportion of the global burden. (15)

Facility-based skilled delivery is inversely correlated to early neonatal deaths and varies widely between and within countries, from 7.2% in rural Burkina Faso to 78% in Senegal. (16) Overall, limited resources and inadequate linkages and standards in the health system undermine maternal-newborn services; transportation is a major constraint to emergency obstetric care in rural communities. (17)(18) Ambulance services, where they exist, are not equipped for transportation of sick newborns. Infants who require postresuscitation care may not receive effective respiratory support during transportation to referral centers and this increases the risk of secondary brain injury.

Published country data on the burden of PA in the subregion are mostly estimates based on inadequate health information systems. In 2010, modeled estimates of population-level data on rates of adverse outcome related to intrapartum events showed an estimated 198,000 intrapartum stillbirths, 129,000 intrapartum-related neonatal deaths, and 173,000 incident cases of NE (Table 1). (6) Unpublished 2017 data from 16 neonatal referral centers in the Republic of Benin, Ghana, and Nigeria show that PA accounted for 30% (range, 14%–58%) of term newborn admissions and 20% (range, 11%–36%) of all neonatal admissions. According to World Health Statistics 2015 from the World Health Organization, intrapartum-related complications among live-born infants caused 8% to 13% of deaths in children younger than 5 years in West African countries. (19)

Survivors of PA in high-income countries have a high risk of impaired neurodevelopmental outcome. (20) Little is known about long-term morbidity among survivors of PA in low-resource settings. (21) Low quality of postresuscitation care has been described in this region and this may increase the risk of severe neurodevelopmental impairment in survivors. (22)

DIAGNOSIS OF BIRTH-ASSOCIATED NE

NE has been described as a clinical syndrome of impaired neurologic function often accompanied by difficulty with initiating and sustaining respiration around the time of birth. (23) Although maternal, placental, and fetal risk factors predispose newborns to NE, intrapartum-related acute hypoxic ischemia is the underlying cause in 50% to 80% of cases in high-income countries and this proportion may be higher in low-resource settings. (24) Antenatal inflammation including chorioamnionitis is common in low-resource settings; this inflammation may potentiate the effects of hypoxia on brain injury and significantly increase the risk for term encephalopathy. (25)

The criteria for attributing a birth-associated hypoxic-ischemic event as the underlying cause of NE have evolved since 1996 but the cornerstone criterion remains the

TABLE 1. **IR Outcomes of NE in West Africa: Estimates for the Year 2010**

COUNTRY	INCOME	BIRTHS	NMR	IR NEONATAL DEATHS	NE CASES	NE NEONATAL DEATHS	NE SURVIVORS (POSTNEONATAL)	NE SURVIVORS MODERATE-SEVERE IMPAIRMENT	NE SURVIVORS MILD IMPAIRMENT
Benin	LIC	350,300	31.8	3,126	3,967	1,051	2,915	840	708
Burkina Faso	LIC	713,200	37.9	7,280	9,322	2,470	6,852	1,973	1,665
Cameroon	LMC	709,900	33.5	6,666	8,404	2,227	6,177	1,779	1,501
Cape Verde	LMC	10,300	14.4	24	61	8	53	15	13
Cote d'Ivoire	LMC	673,100	40.5		9,301	2,465	6,836	1,969	1,661
Gambia	LIC	65,900	31.3	596	737	195	542	156	132
Ghana	LMC	769,700	28	6,054	7,867	2,085	5,782	1,665	1,405
Guinea	LIC	389,900	37.9	4,079	5,102	1,352	3,750	1,080	911
Guinea-Bissau	LIC	58,200	40.1	640	796	211	585	169	142
Liberia	LIC	153,700	34.1	1,478	1,843	488	1,354	390	329
Mali	LIC	714,100	47.7	8,485	11,260	2,984	8,276	2,383	2,011
Mauritania	LMC	116,800	39	1,202	1,565	415	1,150	331	280
Niger	LIC	754,900	32.4	6,500	8,691	2,303	6,388	1,840	1,552
Nigeria	LMC	6,300,000	40	69,240	86,636	22,959	63,678	18,339	15,474
Senegal	LMC	465,400	27.2	3,674	4,650	1,232	3,417	984	830
Sierra Leone	LIC	226,400	45.5	2,708	3,437	911	2,526	728	614
Togo	LIC	193,400	32.4	1,731	2,225	590	1,636	471	397

IR=intrapartum-related; LIC=low income country; LMC=low middle income country; NE=neonatal encephalopathy; NMR=neonatal mortality rate. Source: Lee et al.(6)

presence of severe metabolic acidosis (pH <7.0 and base deficit ≥12 mmol/L) with early signs of moderate or severe encephalopathy. Other minor criteria include a sentinel obstetric hypoxic-ischemic event, abnormal fetal heart rate patterns, low Apgar score, abnormal findings on neuroimaging, and multisystem organ complications. NE is an evolving disorder and no single test or clinical tool is diagnostic. (26)

Acid-base measurements and neuroimaging are not usually available at the point of care in West Africa. Currently, birth-associated NE is diagnosed when a newborn who required resuscitative care at birth presents with abnormal neurologic findings (especially a clinical seizure). Perinatal or birth asphyxia is still the most commonly used terminology. Almost all cases are presumed to be intrapartum-related and other causes of encephalopathy that present around the time of birth are largely underdiagnosed.

Several factors undermine accurate diagnosis of birth-associated NE in the subregion. The skilled workforce and commodities for effective intrapartum monitoring are limited; available tools, particularly the partograph and Apgar scoring, are often not used appropriately or interpreted accurately; and clinical encephalopathy scoring is infrequently used. (27)(28) Integrated perinatal care is not standard practice and newborns referred for postresuscitation care arrive with inadequate information about perinatal events.

The Thompson score, first described in a South African population, is a sensitive early clinical scoring system that has been shown to be sensitive at predicting either abnormal amplitude-integrated electroencephalographic findings or moderate-severe encephalopathy. (29)(30) In Senegal, the modified Sarnat and Sarnat score has been used to diagnose cases of intrapartum-related NE among newborns referred with PA. (31) These approaches suggest that it is feasible to diagnose NE without expensive technology. The scoring tools are easy to use and can be applied as early effective screening tools for birth-associated NE in low-resource settings. Accurate diagnosis of intrapartum-related NE is essential before application of specific therapies because routine application of therapeutic hypothermia may not be safe in the prevailing circumstances in West Africa. Training and supervision of front-line clinicians about the appropriate use of the partograph (or electronic monitoring where available), Apgar score, encephalopathy scoring tools, and checklists (Table 2) to capture intrapartum events and other clinical data may improve the diagnostic accuracy of birth-associated NE.

MANAGEMENT OF BIRTH-ASSOCIATED NE: CURRENT PRACTICE

There is no specific treatment for birth-associated NE, but therapeutic hypothermia reduces death and disability when included as part of a package of neonatal intensive care. (32) However, the safety and efficacy of therapeutic hypothermia in low-resource settings is uncertain. (33) In the West African subregion, the neonatal intensive care package is limited to tertiary centers and a few nontertiary hospitals. In addition to basic newborn care the package includes oxygen therapy, intravenous drugs and infusions including blood products, phototherapy, gavage feeding, and noninvasive respiratory support. Very few centers provide mechanical ventilation. Human resources are severely limited and certified neonatal nurses are rare. Laboratory and radiologic services may not be accessible at the point of care and basic monitoring devices such as pulse oximeters are very limited.

Effective care of newborns with NE requires a well-organized system that provides timely and appropriate supportive care. In rural settings, affected infants may not receive skilled postresuscitation assessment before discharge; it is not uncommon for cases to be referred on the second or third day of age because of poor feeding or seizures. None of the countries in West Africa have specific national guidelines for referral of infants for postresuscitation care. In the few countries with national guidelines for clinical care, the information is scanty and not updated, and some institutional guidelines are not evidence-based. (34)

TABLE 2. **Checklist for Perinatal Risk Factors for Birth-Associated Neonatal Encephalopathy and Related Events**

- Maternal factors
  - Chorioamnionitis
  - Maternal fever >100.4°F (38°C)
  - Prolonged rupture of membranes >18 hours
    - Antibiotics given
    - Antibiotics not given
  - Prolonged hypoxia
  - Prolonged low blood pressure
  - Cardiovascular collapse
- Obstetric complications
  - Umbilical cord prolapse
  - Rupture of the uterus
  - Severe antepartum hemorrhage
    - Placental abruption
    - Placenta previa
  - Placental insufficiency
    - Postdates
    - Scanty liquor
- Fetal factors
  - Abnormal fetal heart rate pattern
    - Persistent fetal tachycardia >160 beats/min >10 min
    - Persistent fetal bradycardia <110 beats/min >10 min
    - Absent baseline variability
    - Recurrent late deceleration
    - Recurrent variable deceleration
- Infant status at birth
  - Inadequate or weak spontaneous respiratory effort
  - Weak or absent cry
  - Resuscitation provided
    - Stimulation or simple oxygen therapy
    - Bag and mask resuscitation
    - Endotracheal intubation

In West Africa, clinicians would generally not provide extra warmth to affected infants during the first 3 days after birth; this practice is described as passive cooling in some countries. For infants with seizures, phenobarbital is the first-line anticonvulsant and phenytoin, where available, is the second-line agent. Some tertiary centers use midazolam infusion for intractable seizures. Concerns about respiratory depression from anticonvulsants limit appropriate treatment of clinically diagnosed seizures. All centers that provide an intensive care package provide postdischarge follow-up care for about 6 to 24 months but the content and quality of the service is variable because there are no national standards. It is not uncommon for families to seek rehabilitation care from spiritual and traditional healers after discharge and only return for hospital care when there is severe disability.

Evidence-based guidelines and clinical pathways may reduce variability in practice and improve quality of services during the acute and rehabilitation stages of care. (35)(36) Limited capacity to continuously monitor body temperature and oxygen therapy is a major constraint. Infants undergoing facilitated endogenous cooling, so-called passive cooling, are at risk for severe hypothermia, hypoxia, or hyperoxia, which may worsen brain injury. Clinical observation, the only method available for diagnosing seizures, is known to be highly inaccurate with low sensitivity; underdiagnosis of seizures increases the risk for brain damage while overdiagnosis may lead to unnecessary and toxic treatments. (37)

RECOMMENDATIONS TO IMPROVE HEALTH OUTCOMES

Reductions in stillbirths and early neonatal deaths from improved intrapartum care and neonatal resuscitation programs may lead to an increase in the population of children and adults with severe disabilities and this has socioeconomic implications for society. (21)(38) Effective implementation of low-cost approaches could prevent some cases of NE, improve the quality of resuscitative and postresuscitation care, and enhance postdischarge rehabilitation services. (27)(39) This section provides general recommendations that can be adapted to local circumstances.

Community Engagement

Of the 3 major causes of neonatal death, PA is the least understood by communities in West Africa. Cultural beliefs and myths about pregnancy and birth-associated injuries affect health-seeking behavior for facility-based delivery and postdischarge rehabilitative care. Improving the health literacy of mothers and families about the risk and socioeconomic consequences of PA and benefits of acute and rehabilitative care is critical to reducing the burden of disease. (27)(39) An increasing number of women in the subregion are receiving antenatal care services in health facilities; this offers an opportunity for providers to improve the health literacy of mothers and communities on birth-associated injuries.

Effective community engagement has the potential to significantly reduce demand-side barriers to facility-based care. (40) Engaging traditional, political, and religious leaders, as well as social groups of women and men in rural communities, as advocates for reducing PA and severe disability will reduce cultural barriers to care seeking. The tradition of restricting pregnancy-related information to only women needs to change. Community health services should create opportunities to educate men about PA; the “School for Husbands” in Niger is a program worth emulating. (41) Where limited access or cultural resistance to facility-based care is a constraint, integrating traditional birth attendants into the health system should be considered because this approach has improved maternal-newborn outcome in Sierra Leone and other African countries. (42)

Improve Referral Systems and Integrate Care

No single referral system can meet the needs of all communities; lessons can be learned from diverse approaches to improve referral systems for emergency maternal-newborn care. (43) Rural community efforts and social media platforms are bridging some gaps in maternal services. These approaches can be extended to newborns when intrauterine transfer is not possible. Adequate oxygen therapy and respiratory support should be provided throughout the journey from the labor room to the neonatal unit. Every birthing place should have a newborn

TABLE 3. **Content of Newborn Transport Kit**

Bag and mask equipment (appropriate sizes)
Portable suction device and accessories
Oxygen: Small oxygen cylinder with blender, oxygen delivery tube with face mask or nasal prongs
Pulse oximeter
Thermometer
Glucometer
Stethoscope
Intravenous cannula sizes 24G, 26G
Syringes and needles: 2 mL, 5 mL
Intravenous infusion set
Nasogastric tube sizes 5–8F
Intravenous infusions: D10W, normal saline
Thermal care: Cot sheets, blankets, cap
Medications: Epinephrine, phenobarbital, naloxone, calcium gluconate 10%
Hygiene supplies: Gloves, alcohol wipes, diapers, cotton wool
Other advanced equipment and supplies depending on available expertise

transport kit (Table 3) containing appropriate sizes of bag and mask and other supplies. If an ambulance or other forms of vehicular transport service exist, efforts should be made to equip them to meet basic needs, especially respiratory care, of sick newborns.

Formal communication between obstetric and pediatric services should extend beyond monthly or quarterly perinatal mortality meetings, and providers of neonatal care need to engage with rehabilitation service providers. Effective communication and collaboration between departments is essential. An integrated approach to perinatal care may improve diagnostic capacity and management for affected infants. (36)(44) Hospitals that offer comprehensive obstetric care should have a pediatric team responsible for the newborn around the time of birth. Limited human resources pose a major handicap at district hospitals where most births occur; many facilities may have 1 medical officer or pediatrician responsible for all neonatal and pediatric cases. However, a pediatric team of skilled nurses/midwives equipped with guidelines and checklist (Table 2) could provide this service under the supervision of a single physician.

Good-Quality Clinical Care

Many facility-based birth attendants in the subregion have not received NRT, and basic resuscitation equipment is not available at the point of care. (45) With central government support, national pediatric/neonatal societies have the pivotal role of formulating national guidelines, training birth attendants, and possibly instituting a national NRT program. Advocacy for essential equipment and supplies for newborn services is vital. Other approaches to improving essential care and resuscitation around the time of birth have been described. (46)

Infants with birth-associated NE are at high risk of having a secondary brain injury from secondary hypoxia and hyperoxia, hypocapnia and hypercapnia, untreated and prolonged seizures, sepsis, hyperthermia, and excessive (<91.4°F [33°C]) and prolonged cooling (>72 hours). Lessons can be learned from high-income countries over the last decade, with neonatal neurocritical care emerging as a culture change toward a “brain-focused” approach to mitigate secondary brain injury, rapid recognition of complications and seizures, consistent use of protocols, and use of experienced teams. There is an urgent need for a culture change in the practice of neonatology in West Africa, including a culture of teamwork and continuous quality improvement in the organization and practice of neonatal care.

A culture change in West African neonatal care will require basic training in measures to prevent secondary brain injury and use of affordable and durable diagnostics, including simple amplitude-integrated electroencephalography devices to improve the diagnosis of seizures, especially in tertiary centers. Affordable and durable pulse oximeters and acid-base measurement equipment may improve the quality of care and health outcomes. Other options for anticonvulsant therapy for NE need to be considered because phenobarbital and phenytoin may not effectively treat neonatal seizures. (47)

Facilitated endogenous cooling (ie, passive cooling) is currently standard practice in most West African countries. Central cooling, the endogenous physiologic response to asphyxia, was observed in infants in 1958 by Burnard and Cross and recently in a pilot randomized trial in Uganda. (48)(49) The cooling response may be exaggerated and prolonged in infants with severe NE. It is unclear whether this endogenous cooling response is as neuroprotective as therapeutic hypothermia; also, the effect of antenatal inflammation on endogenous cooling is unknown. Concerted efforts should focus on reducing secondary brain injury until local randomized trials provide evidence for other therapies.

FUTURE INTERVENTIONS AND RESEARCH

Countries need to adopt continuous quality improvement initiatives and use available resources more efficiently. Tertiary institutions or countries should consider joining established neonatal networks. Collaborative networks provide opportunities for improving standards, learning, research collaborations, data-driven quality improvement, and more. Ethiopia has recently joined the Vermont Oxford Network and other countries can learn from Ethiopia’s experience. The West African Health Organization should recognize and prioritize the burden of birth-associated NE, advocate for improved neonatal services, and possibly facilitate a regional collaborative neonatal network.

TABLE 4. **Future Needs and Direction for Improving Care**

- National center of excellence that provides an intensive care package including neurocritical care to scale up national training
- Affordable effective technologies and drugs for accurate diagnosis and management of neonatal seizures
- Improved capacity for effective rehabilitative care especially at district level

Parenteral levetiracetam, commonly used for neonatal seizures in high-income countries is expensive and not available in the subregion. Safer, effective, and affordable drugs for neonatal seizures will reduce morbidity. Feasibility of conducting randomized clinical trials using newer anticonvulsants for newborns in the subregion should be explored.

Accurate diagnosis of antenatal inflammation in the subregion is a challenge. Research on rapid diagnostic tests is needed. The effect of endogenous physiologic cooling should be investigated in a randomized controlled trial in a setting with a high burden of disease. Future needs and direction for improving quality of care and outcome for birth-associated NE in West Africa are summarized in Table 4.

SUMMARY

- There are major gaps in the health system of West African countries that inevitably result in high burden of neonatal deaths and disability from perinatal asphyxia.
- Expensive technologies are not required to reduce the high burden of death and disability; engaging communities and improving timely access to quality maternal-newborn services is essential.
- New technologies and therapies will improve the diagnosis and management of newborns with birth-associated neonatal encephalopathy but the primary goal should focus on prevention.
- Quality improvement interventions should address the organization and culture of clinical care.
- More research on safer anticonvulsants and endogenous and therapeutic cooling is needed.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical features, diagnosis, and management of perinatal hypoxic ischemic encephalopathy.
- Know the issues in the organization of perinatal care (e.g., regionalization, transport, practice guidelines, benchmarking data, quality improvement).

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Neonatal Antibiotic Use: What Are We Doing and Where Shall We Go?

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Education Gap

To properly assess the scope of the problem of unnecessary antibiotic use and monitor the impact of such efforts, there is a need to consistently characterize antibiotic usage in NICUs and nurseries, as well as among centers.

Abstract

Antibiotic stewardship aims to ensure that clinicians administer the right antibiotics, to the right patients, for the right reasons. These principles are being widely applied in medical care, but have been particularly challenging in the NICU. Infectious risk factors and clinical instability are common among neonatal patients, and lead to significant cumulative antibiotic exposures in the NICU setting. Both the frequency with which antibiotics are administered and the potential unintended consequences of antibiotic administration differ between preterm and term infants. Multiple metrics are available to measure antibiotic use, yet no single measure is universally applied to neonatal stewardship.

Objectives

After completing this article, readers should be able to:

1. Review current rates of neonatal antibiotic use among preterm and term infants.
2. Recognize the potential risks of antibiotic therapy in preterm and term infants.
3. Describe measures of antimicrobial stewardship and identify advantages and limitations of applying these to the neonatal population.

INTRODUCTION

Antibiotic therapy is a mainstay of neonatal care, and antibiotics are the most commonly prescribed class of medications in the NICU. (1)(2) Antibiotics have

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ABBREVIATIONS

AAP	American Academy of Pediatrics
AUR	antibiotic use rate
BPD	bronchopulmonary dysplasia
CDC	Centers for Disease Control and Prevention
DOT	days of therapy
ELBW	extremely low-birthweight
EOS	early-onset sepsis
NRN	Neonatal Research Network
VLBW	very low-birthweight

clear benefits for infants with suspected or confirmed infection, but appropriate narrow-range coverage and treatment durations remain an issue. (3) However, there is increasing evidence pointing to the risks of adverse outcomes of antibiotic exposure among infants without culture-confirmed infection. Measures to improve both prevention of infection and accuracy in diagnosing infection should result in decreased antibiotic use. To measure and ultimately optimize antibiotic use, there is a need to consistently characterize antibiotic use in NICUs and nurseries, as well as across centers. A thorough understanding of current antibiotic use and reliable tools for measuring use are first and critical steps to appropriately applying the principles of antimicrobial stewardship to the neonatal population.

ANTIBIOTIC USE AMONG PRETERM INFANTS

Preterm infants frequently receive empirical treatment with antibiotics soon after birth because of the risk of early-onset sepsis (EOS). Preterm labor and/or premature rupture of membranes result from maternal infection in about a third of cases, (4)(5) and 1 in 90 very low-birthweight infants (VLBW; birthweight <1,500 g) is diagnosed with culture-confirmed EOS. (6) The infection-attributable mortality among VLBW infants with EOS is ~35%, and ranges as high as 50% for infants at the lowest gestational ages (22–24 weeks). (7) Given the relatively high prior probability of EOS and the staggering risk of mortality, combined with the clinical instability inherent among preterm infants at birth, (8) it is no surprise that the rates of empirical early antibiotic therapy among preterm infants are quite high.

Neonatal clinicians also frequently extend antibiotic therapy despite sterile cultures for various reasons. Clinicians express concern that maternal intrapartum antibiotics, inadequate blood volumes for neonatal culture, and/or neonatal antibiotics administered before blood culture may all result in false-negative findings. Perhaps most important, clinicians are reluctant to stop antibiotic therapy when preterm infants remain critically ill. In a study of 790 extremely low-birthweight (ELBW; birthweight <1,000 g) infants born in 2000, 94% received early empirical antibiotics and 59% received more than 3 days of therapy despite negative blood culture findings. (9) In a larger study including approximately 4,000 ELBW infants born in Neonatal Research Network (NRN) sites from 1998 to 2001, 96% received early empirical antibiotics and 53% received more than 4 days of therapy despite negative cultures. (10) Kuppala et al found that in VLBW infants without sepsis or necrotizing enterocolitis (NEC) who survived past day 7, 36% (130/365) received prolonged initial empirical antibiotics for 5 days or more. (11) A study from the Canadian Neonatal Network reported that of 8,414 VLBW infants without infection-related morbidities, 4,607 (55%) received antibiotics for 4 or more days in the first week of age. (12)

We recently examined early antibiotic use among preterm infants over time and across both academic and community hospitals in the United States. (13) Of 40,364 VLBW infants, including 12,947 ELBW infants, the majority received antibiotics in the first 3 days after birth (79% of VLBW; 87% of ELBW) and no differences in antibiotic initiation were observed over time from 2009 to 2015. Rates of VLBW infants receiving more than 5 days of early antibiotics decreased slightly over time, but did not change among ELBW infants, with significant variation in practice observed across centers. Overall, rates of antibiotic treatment in preterm infants in the first days after birth are an order of magnitude higher than the actual incidence of culture-confirmed early infection, and little change has been observed over time. (6)(14)(15)

Current guidance on antibiotic use for preterm infants is to use antibiotics in all newborns with critical illness. (16) Recent studies suggest that EOS risk assessment strategies for preterm infants could be based on delivery characteristics and/or placental pathologic findings that correlate with culture-confirmed infection. (17)(18) Currently, no well-developed EOS risk assessment tools are available for VLBW infants as exist for term newborns. (19)(20)

Most studies of antibiotic use in preterm infants have focused on the first days after birth; there are fewer data regarding antibiotic use in preterm infants during the entire hospitalization because these infants are often grouped together with term infants in analyses of overall unit-specific antibiotic use. A 1998 to 2000 multicenter study from the United States reported that 56% of VLBW infants (3,459/6,215) received at least 1 antibiotic course after postnatal day 3. (21) Among 13,738 infants cared for in Canadian centers from 2010 to 2014, 11,669 (85%) received antibiotics at any point during hospitalization. This study did find a decline in antibiotic use over the entire NICU hospitalization: the overall annual antibiotic use rates (AURs), defined as number of days an infant was exposed to 1 or more antibiotics divided by the total length of stay, declined from 0.29 in 2010 to 0.25 in 2014. (12)

ANTIBIOTIC USE AMONG TERM INFANTS

Rates of antibiotic exposure for suspected EOS among term newborn infants vary by center. (22)(23) Although center variation could be related to differences in obstetric practice or in rates of maternal intrauterine infection, the primary factor identified in a recent national survey of newborn practice is variation driven by evolving methods of EOS risk assessment. (22) Measurement of AURs among term infants may also be complicated by the fact that there is center-specific variation in how such infants receive care. For example, well-appearing newborns receiving antibiotic therapy in the NICU will be counted in NICU-specific AURs, while similar infants receiving these therapies in a nursery setting, or while rooming-in with the mother, will be missed.

As many as 400,000 uninfected newborns are administered empiric antibiotic therapy at birth for the risk of EOS every year in the United States. (19)(24) In a population-based study by Escobar et al, 15.2% (2,785 of 18,299) of infants with birthweights greater than or equal to 2,000 g were evaluated for EOS, and of these, 31% were treated with systemic antibiotics. (25) Another center using a local algorithm based on Centers for Disease Control and Prevention (CDC) 2002 guidelines found that 15% of well-appearing newborns of 35 weeks' gestation or greater were evaluated for EOS. (26) After adjusting policies based on updated CDC 2010 guidelines, the same center found that 6.8% of all well-appearing infants born at more than or equal to 36 weeks' gestation were evaluated for EOS and 5.2% were treated with empiric antibiotic therapy, while only 0.04% of the study cohort had culture-confirmed EOS. (26) Multivariate risk models may significantly decrease the number of EOS evaluations in term and late preterm newborns and decrease empiric antibiotic exposure in this population. (19)(20)(27) Prospective studies using a neonatal sepsis risk calculator based on these models demonstrated 40% to 50% decreases in empiric antibiotic administration to term and late preterm infants compared with prior practices, and found no safety concerns. (28)(29) Only 2.6% of all infants born at more than or equal to 35 weeks' gestation in the perinatal centers of the Kaiser-Permanente Northern California healthcare system received empiric antibiotic treatment with the use of the sepsis risk calculator combined with locally derived care algorithms. (28)

Recommendations regarding duration of antibiotic therapy for suspected EOS also continue to evolve. (30)(31) Kiser et al reported in 2014 that at their institution, based on American Academy of Pediatrics (AAP) practice guidelines at the time, 24.2% of term and late preterm infants at risk for EOS due to maternal chorioamnionitis received antibiotics for more than or equal to 7 days. (32) The vast majority of these infants were treated with prolonged antibiotics because of abnormal laboratory values alone. Later revisions to the AAP guidelines recommend against treating asymptomatic infants with sterile cultures born to mothers treated for chorioamnionitis longer than 48 to 72 hours. (33)

There are fewer data on AURs specifically for term infants after the EOS period. In a 2005 national point prevalence study of 29 American centers, 43% of NICU patients were receiving antimicrobial therapy on the date of the survey. (1) In a 2013 study of 127 NICUs across California, which included both term and preterm infants, 40-fold variation in overall AURs was reported, and this variation was independent of burden of infection. (34)

RISKS OF ANTIBIOTIC THERAPY FOR PRETERM INFANTS

Multiple studies suggest that antibiotics have potential risks for preterm infants without culture-confirmed infection. Broad-spectrum antibiotic exposures, particularly cephalosporin use, have been identified as problematic. Cephalosporin use is associated with increased incidence of invasive fungal infections in preterm infants, (35)(36) with an attributable mortality of 13%. (37) In a multicenter study that included 128,914 newborns of all gestational ages, empiric early treatment with a combination of ampicillin and cefotaxime, compared with ampicillin and gentamicin, was associated with higher mortality rates. (38)

Perinatal and postnatal antibiotic exposures are also associated with subsequent colonization with resistant bacterial organisms and later infection. (39)(40)(41)(42)(43) Most studies conducted in preterm infants have focused on the potential link between overall antibiotic exposures and later morbidities and mortality. One study of 5,693 ELBW infants cared for in 19 NRN centers found an association between prolonged initial antibiotic therapy (defined as antibiotics initiated at <3 days of age and continued for ≥ 5 days) and subsequent risk of NEC or death. (10) Prolonged initial empiric antibiotic use in VLBW infants cared for at 3 sites in Cincinnati, OH, was associated with the combination of late-onset sepsis, NEC, or death. (11) In a single-center study of 1,140 VLBW infants, each additional day of antibiotic exposure in the first 14 days of age was associated with increased risk of death or bronchopulmonary dysplasia (BPD), as well as increasing severity of BPD. (44) The relationship between early antibiotic exposure and development of NEC or BPD has been reported in other settings (39)(45) and may have biologic plausibility in a link between antibiotic exposure and subsequent gastrointestinal and airway microbiome dysbiosis. (43)(46) The Canadian multicenter study of VLBW infants without culture-confirmed infection or NEC found an association between infants in the highest AUR quartile and a composite outcome of mortality or "major morbidity" including persistent echogenicity or echolucency on neuroimaging, stage 3 or higher retinopathy of prematurity, or BPD. (12)

The association between the higher AURs and the composite outcome in this study was largely driven by the substantial increase in mortality among these infants. The primary limitation in all of these studies is confounding by indication: sicker infants are more likely to receive antibiotics than infants who are less sick, though each study included statistical adjustment for factors associated with severity of illness. The consistent association of poorer outcomes with empiric antibiotic exposure across studies of various designs and study cohorts suggests that prospective studies of antibiotic administration in the absence of culture-confirmed infection may be justified.

RISKS OF ANTIBIOTIC THERAPY FOR TERM INFANTS

In many centers, term infants are admitted to the NICU when empiric antibiotic therapy is indicated. For well-appearing asymptomatic infants, there is a potential negative impact of maternal/infant separation on initiation and exclusivity of breastfeeding. (30)(47) In the NICU, newborns are also at increased risk of exposure to multidrug-resistant organisms and nosocomial infection. (48) These risks may be mitigated if infants requiring intravenous antibiotics can receive the therapy in the mother's postpartum care setting. (49)

Early antibiotic exposure may initiate dysbiosis even among otherwise healthy term infants. There is evidence that early life antibiotics alter gut and airway microbiota. (46)(50)(51) The widespread use of antibiotics during the peripartum (eg, intrapartum and immediate neonatal) period and the demonstration that such exposures alter the initial composition of the newborn gut microbial composition raises the possibility that intrapartum preventive therapies may have later health consequences. (52) These concerns are supported by studies of early infancy and childhood antibiotic exposures. Canadian infants receiving antibiotics in the first year of age were more likely to be overweight in childhood. (53) In a Finnish population based-cohort, antibiotic exposure before 6 months of age or repeatedly during infancy was associated with increased body mass in early childhood, with a distinct relationship between broad-spectrum antibiotic exposure and subsequent increased body mass. (54)

Studies also suggest a relationship between early antibiotic exposure and subsequent development of asthma. (55)(56)(57) Asthma is the most common childhood chronic illness, with increasing prevalence over the last 4 decades. (58) Using a longitudinal birth cohort of infants in British Columbia born between 1997 and 2003, investigators found that use of antibiotics in the first year of age was associated with increased risk of developing asthma and that the risk increased as the number of antibiotic prescriptions increased. (58) A systematic review of multiple studies addressing antibiotics administered in infancy and risk of childhood asthma found a pooled odds ratio of 1.52 (95% confidence interval [CI], 1.30–1.77). (55) Multiple confounding factors may influence the relationships between early antibiotic exposure and subsequent obesity, asthma, or allergic disease. Prospective studies of maternal, preterm, and term infant antibiotic exposures and the impact on childhood outcomes are ongoing and will better inform the true risks and benefits of empiric antibiotic use in the perinatal and early life period. (59)

NEONATAL ANTIMICROBIAL STEWARDSHIP

In 2002, the CDC proposed 12 steps to prevent antimicrobial resistance, based on 4 key strategies: preventing infection, diagnosing and treating infection effectively, using antimicrobial agents wisely, and preventing transmission of drug-resistant pathogens. (60) The antimicrobial stewardship elements of this campaign are relevant to NICU settings, yet are infrequently applied. (61) The Table summarizes the core elements of antibiotic stewardship recommended by the CDC and applicable to NICU settings. Antimicrobial stewardship efforts and national quality improvement initiatives have started to focus on neonatal settings, but there is continued uncertainty among neonatal clinicians about the optimal application of antimicrobial stewardship principles. (62)(63)(64)

Longitudinal accounting of antimicrobial use is a particularly important part of stewardship. To assess antimicrobial use in NICUs and nurseries and track change over time, there is a need to consistently characterize antibiotic use in these units and among certain populations. A detailed understanding of how antibiotics are used among specific categories of newborns may help optimize stewardship efforts. Currently, there are no uniformly accepted metrics of neonatal antimicrobial usage. For instance, some studies report proportions of infants who are started on antibiotics soon after birth, some report number of antibiotic courses during hospitalization, and others simply report proportions of infants in the NICU receiving antibiotics at a given point in time. Prolonged duration of empiric antibiotic treatment after a blood culture specimen is obtained may be defined as beyond 48 hours, 72 hours, 5 days, or even 7 days in different studies. Some studies report any exposure to any antimicrobial drug and some delineate by specific drug, class, or combination.

TABLE. **Interventions to Improve Neonatal Antibiotic Use**

INTERVENTION	DESCRIPTION
Broad interventions	
Antibiotic "time outs"	Review of antibiotics 48 hours after initiation to actively determine extension or discontinuation
Prior authorization	Restricted use of certain antibiotics based on spectrum of activity, cost, or toxicities
Prospective audit and feedback	External review of antibiotic appropriateness by an expert in antibiotic use
Facility-specific treatment recommendations	Development and implementation guidelines based on site-specific patient characteristics and local antimicrobial susceptibility data
Pharmacy-driven interventions	
Dose adjustments and optimization	Guidance based on gestational and/or postnatal age, organ dysfunction, therapeutic drug monitoring, resistance profile, etc
Automatic alerts	Reminders often embedded in electronic order entry systems For example, alerts may flag unnecessarily duplicative therapy; drug-drug interactions; or warnings based on patient characteristics (eg, renal or liver dysfunction)
Time-sensitive automatic stop orders	Stop orders useful for specified antibiotic prescriptions and indications, especially antibiotics administered for surgical prophylaxis
Tracking and reporting antibiotic use and outcomes	
Antibiotic use measures	
Defined daily dose	Estimation of antibiotic use in hospitals by aggregating the total number of grams of each antibiotic purchased, dispensed, or administered during a period of interest divided by the World Health Organization–assigned daily defined dose; not appropriate for neonatal settings
Days of therapy	Aggregate sum of days for which an antibiotic is given to a patient (numerator) divided by a standardized denominator (eg, patient days)
Antibiotic use rate	Number of days an infant was exposed to 1 or more antibiotics divided by the total length of stay
Variation in use	Comparison between institutions combined with information on infection burden and case mix
Outcome measures	
Clinical outcomes	Specifically, outcomes that measure the impact of interventions to improve antibiotic use (eg, duration of bacteremia, metastatic complications of infection, mortality)
Antibiotic resistance	Systematic accounting and display of local antimicrobial resistance data for both colonizing and infecting pathogens
Annual drug cost savings	Comparison of pre- and post-implementation costs of stewardship programs and/or interventions

Adapted from Centers for Disease Control and Prevention. Core elements of hospital antibiotic stewardship programs. Available at: https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html. Accessed June 11, 2018.

Measures and metrics to study the impact of antimicrobial stewardship programs have been reported for other populations. (64) The most commonly used measures evaluate drug consumption. Among studies conducted in adult patients, a widely accepted measure is "defined daily dose," which is the amount of drug that a typical patient might receive on any day for therapeutic purposes. This measure is impractical in pediatric and neonatal populations because of the weight-based dosing required in these patients. Another method commonly used in antimicrobial stewardship research is to evaluate drug consumption by days of therapy (DOT). DOT is defined as overall days of antimicrobial therapy, usually reported per 1,000 patient days. DOT accounts for multiple drugs, for example, an infant receiving 2 antibiotics for 7 days contributes 14 DOTs. This measure may indirectly incentivize providers to use broad-spectrum monotherapy (ie, an infant receiving 1 broad-spectrum antibiotic for 7 days only contributes 7

DOTs), but overall is broadly applicable to many populations including neonates. (65) AURs, defined as the number of days an infant was exposed to 1 or more antimicrobial agents divided by the total length of hospital stay, have recently been used as a metric of antibiotic use in the NICU. One limitation of this metric is that it is influenced by the mortality rate, because less time to death will result in a higher AUR. Optimal AURs in the NICU are not defined, and it remains unclear how AURs may be influenced by NICU type and case mix. (34) In addition, general AUR studies do not discriminate between narrow- and broad-spectrum antibiotics. Variation as a measure of antibiotic use in NICUs may be helpful, particularly when information on infection burden and case mix are available. Variation in the absence of infection among centers with similar morbidity and mortality profiles suggests that some proportion of antibiotic use may be unnecessary and may be used to identify target interventions for potentially modifiable prescribing behaviors. (34)

An important component of neonatal antimicrobial stewardship is to report the incidence of antimicrobial resistance among colonizing and infecting pathogens. A common approach involves reporting rates of specific resistant organisms such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. A broader approach involves reporting and communicating antimicrobial-sensitivity data to inform stewardship interventions. Finally, clinical outcomes including local rates of early-onset and late-onset infection as well as short-term infection-related morbidity and mortality must be considered in designing and assessing the impact of local antimicrobial stewardship interventions.

CONCLUSIONS

- Antimicrobial stewardship efforts have started to focus on neonatal settings.
- Multiple recent studies suggest that antibiotics have potential risks as well as benefits for both term and preterm newborn infants.
- To properly design and monitor neonatal antimicrobial stewardship efforts, there is a need to consistently characterize antibiotic use in NICUs and nurseries, as well as across centers.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know how infectious agents are transmitted to the neonate.
- Understand the treatment and complications of sepsis.
- Know the infectious agents that cause neonatal sepsis.
- Know the maternal, perinatal, and neonatal risk factors for neonatal sepsis.
- For antibiotics used commonly in the neonate, know indications for their use, clinical effects, pharmacokinetics, side effects, and toxicity,

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1. Early-onset sepsis (EOS) is a common concern for preterm infants because preterm labor and/or premature rupture of membranes results from maternal infection in about a third of cases. What is the proportion of very low-birthweight (VLBW) infants who are diagnosed with culture-confirmed EOS?

   A. 1 in 20.
   B. 1 in 50.
   C. 1 in 90.
   D. 1 in 120.
   E. 1 in 200.

2. The rates of antibiotic exposure for suspected EOS among term and late preterm newborn infants vary by center. The use of multivariate risk models such as a neonatal sepsis risk calculator has been shown to decrease empiric antibiotic exposure in this population. In prospective studies using the neonatal sepsis risk calculator, rates of empirical antibiotic administration decreased by:

   A. 10%–20%.
   B. 20%–30%.
   C. 30%–40%.
   D. 40%–50%.
   E. 50%–60%.

3. Multiple studies suggest that antibiotics have potential risks for preterm infants without culture-confirmed infection. The use of cephalosporin, in particular, has been identified as problematic. Of the following, what risk is specifically associated with cephalosporin use?

   A. Increased risk of subsequent necrotizing enterocolitis.
   B. Increased risk of death or bronchopulmonary dysplasia.
   C. Increased risk of asthma.
   D. Increased incidence of invasive fungal infections.
   E. Increased risk of stage 3 or higher retinopathy of prematurity.

4. Antimicrobial stewardship is a critical element in preventing antimicrobial resistance. One of the metrics used to study the impact of antimicrobial stewardship programs is the drug consumption by days of therapy (DOT). DOT is defined as:

   A. The overall days of antimicrobial therapy per 1,000 patient days.
   B. The number of days an infant was exposed to 1 or more antimicrobial agents divided by the total length of hospital stay.
   C. The sum of days for which any amount of a specific antimicrobial agent is administered per 1,000 days present.
   D. The number of days an infant was exposed to a specific antimicrobial agent divided by the length of stay.
   E. The overall days of antimicrobial therapy per length of stay.

5. Measures and metrics are important considerations when studying the impact of antimicrobial stewardship programs. Metrics traditionally used in adult populations do not always apply to neonatal populations. Annual antibiotic use rates (AURs) have recently been used as a metric of antibiotic use in the NICU. Which of the following statements is correct regarding the limitations of AURs?

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A. This measure may indirectly incentivize providers to use broad-spectrum monotherapy.
B. This measure is impractical in neonatal populations because of the weight-based dosing required in these patients.
C. This metric is influenced by mortality rate, because shorter time to death will result in a lower AUR.
D. This metric discriminates between narrow- and broad-spectrum antibiotics.
E. Optimal AURs are not well defined in NICU populations.

NICU Communication: The Many Disguises of Opportunity

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Education Gap

A lack of effective communication in the NICU can inhibit improvement and overall collaboration between the medical team and the infant's family.

Abstract

In the NICU, communication with parents, family, and other members of the care team is extremely important. Multiple issues can impede effective communication around goals of care, particularly in the context of end-of-life discussions. This review looks at a select few of those difficult topics and identifies them as opportunities for deeper and more productive discussions with parents of critically ill neonates as well as medical staff.

Objectives After completing this article, readers should be able to:

1. Discuss the importance of effective communication.
2. Recognize the opportunity for exploring the concept of "everything."
3. Recognize the opportunity for exploring the concept of "hope."
4. Realize that certain phrases, such as "withdrawal of care," can shape a communication culture.

INTRODUCTION

The designation *NICU* aptly describes the atmosphere of this highly specialized unit. The intensity of care provided by a health-care team using the most advanced medical technology to care for medically fragile newborns is compounded by the emotions experienced by families. Depending on the reason for the NICU stay, families may face a variety of complex emotions, including fear that the infant will die or survive with impairments; loss of their hope for a healthy term birth and of control over their family future; guilt that they somehow contributed to the infant's situation; and frequently, a mixture of anger, frustration, and gratitude

AUTHOR DISCLOSURE Drs Niehaus and Maurer have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

toward the NICU staff. Faced with an often uncertain prognosis, the NICU environment becomes frightening and stressful for many families. (1)(2)

Given these many complexities, effective communication is an essential component of NICU care. Communication with the family is mediated by multiple persons in the NICU, including nurses, specialty care providers (eg, respiratory therapists, nutritionists, lactation consultants, physical therapists), and other families. In this review, we will focus on the role of the physician in NICU communication. Because family supports are often complex, we will use the term "family" rather than "parent."

The manner in which a physician communicates with an anxious family of an infant admitted to the NICU may determine both what the family understands and how they subsequently interact with the other members of the health-care team. Despite the importance of skilled communication in such situations, NICU physicians and trainees do not frequently receive education in such skills. (3)(4) Yet there are specific words and phrases used by both families and medical caregivers in high-stress situations that may not be optimal and may even be polarizing. Common examples are: "The parents want everything done," "I don't want to take away their hope," and "withdrawal of care." Phrases such as these may immediately shape how families and caregivers view the conversation—and each other. These phrases may inadvertently discourage the exchange of feelings and ideas rather than facilitating communication and neonatal care.

Using specific examples, this review will focus primarily on 2 aspects of communication: 1) How the physician's choice of language influences how the conversation is received by families; 2) How the physician's choice of language influences the perceptions of other members of the health-care team. We will explore the possible responses to the family stating that they want "everything done," or are "hoping for a miracle." These phrases may immediately imply to the physician that the parents "didn't get it," or seemed "unwilling to accept" a poor prognosis. How do we use these phrases to begin a more nuanced conversation about family values and choices, and communicate this to other providers? This review of current adult and pediatric palliative care literature seeks to shed some light on these difficult yet influential conversations.

"THEY WANT EVERYTHING"

> *A 35-year-old gravida 1, para 0 pregnant woman with no significant medical history is about to give birth to a term infant with known trisomy 13 and complex congenital heart disease. The neonatologist, never having met the woman, wants to determine her goals of care for her neonate. The neonatologist counsels her about outcomes of neonates born with trisomy 13. She tearfully looks up at the neonatologist and says: "Please do everything for my baby!"*

"Everything" may be the most emotionally laden word in NICU communication. The context of the phrase is nearly as varied as its possible meanings. It is often uttered during shift hand-offs, from physician-to-physician or nurse-to-nurse: "This family wants everything." Or, as in the described case, the family addresses the care team: "We want everything done." The family rarely wants *everything* simply for the sake of wanting everything (5) yet many times that is the assumption without exploring the family's true meaning. This can perpetuate an ambiguous plan of care.

> *Physician: Unfortunately, your child is not responding to the treatment as we had hoped.*
> *Parent: We want you to do everything.*
> *Physician: Ok. We will do everything.*

"Everything" can designate many things, but it is often an impediment to an exploratory conversation. Individual physicians carry their own definition of "everything" that is not universal, but usually is influenced by the specific patient and clinical situation. When the physician decides that the mere word "everything" means that the family wishes for the physician's version of "everything" in a given situation, it is likely to lead to misunderstanding and conflict. The assumptions made in this scenario may be adopted by the full medical team. The care team after a while may conclude that the family wants their child to be a "full code" and are in favor of myriad interventions that they may not fully understand, each of which may have an uncertain impact on the infant's condition.

An alternate approach is for the physician to use the word "everything" as a starting point to uncover the family's values, hopes, and fears, and begin a nuanced conversation to arrive at informed goals of care.

> *Physician: Unfortunately, your child isn't responding to the treatment as we had hoped.*
> *Parent: We want you to do everything.*
> *Physician: It is so scary to think he may not survive this. You have been such loving parents throughout this time. I wonder if you would be willing to share with me what you are hoping for?*

In this version, the physician recognizes the emotion behind "everything" and addresses it with 2 empathetic statements: *It is so scary to think he may not survive this. You have been such loving parents throughout this time.* Once the physician attends to the emotions behind the parent's desire for "everything," fears can be addressed and, hopefully, goals of care can be set cooperatively. (6)(7)

Fear may be the driving force behind the family wanting "everything." (5)(8)(9) The fear could be of abandonment stemming from a binary view of health-care delivery: everything or nothing. (8) Families may feel that if the medical team is not doing "everything for my child," then they have "given up" on the child and on the family. The family may not want a multitude of surgical procedures that add little to the length or quality of that infant's life, but they prefer such a plan of care to a plan of perceived abandonment. This approach of "everything" may lead to conflict and distress amongst the parents and the whole medical team as their perceptions of the benefits and burdens of care become increasingly divergent. Polarization can feed on itself: the family may become more vocal and agitated about wanting "everything" while the care team becomes more frustrated with a family fighting for "futile care."

Fundamentally, families fear a worsening illness leading to the death of their infants. The NICU medical team cannot forget that the family has 1 short-term priority—the family does not want their child to die. (8) "Everything" may be a plea to make the finality of death not a reality. An individual family member who has realized that the infant is dying may be making an emotional appeal for support as opposed to a cognitive request for extensive therapeutic measures. In such cases, recognition of a family's anguish and assurance of nonabandonment is more effective than offering futile interventions. Simply agreeing to do "everything" and not exploring this response encourages the family to continue to deny worsening illness. (5)

The fear of death does not solely exist within the family. The physician may be reluctant to deliver bad news, and may fear the technical and emotional complexities of end-of-life discussions. Intensive care physicians often lack formal training in such conversations despite the frequency with which they must be conducted. Importantly, the physician may consciously or unconsciously ascribe to the binary misconception that "death" equals "failure." By assuming an understanding of what is behind a family's plea for "everything," the physician may delay or entirely avoid the conversations that he or she may dread. (9)

"Everything" should not be an end, but rather a beginning. (5)(9) "Everything" should be treated as an opportunity to explore the family's values, emotions, biases, and ultimately their goals of care for their child. Taking advantage of the opportunity "everything" provides should lead to better communication, less distress for both families and care teams, and better care more aligned with families' true goals of care.

"I DON'T WANT TO TAKE AWAY THEIR HOPE"

A 2-week-old male infant is born at 23 weeks' gestation to a 38-year-old gravida 1, para 0 woman who conceived via in vitro fertilization. Since birth, his clinical condition has slowly worsened. He is now on extremely high ventilator settings on the high-frequency oscillator, requiring a fraction of inspired oxygen of 1.0. The mother and father have rarely left the bedside during their child's admission. On rounds, the parents ask, "He's going to be ok, right?" Not wanting to crush the couple's hope, the clinician responds, "We just have to get him to grow. His electrolytes are improved from yesterday, which is good news."

Another concept physicians and families struggle with is hope. Hope is not only an important part of medical care for families, it is a key aspect of all our lives. What hope means to each individual is highly personal and may focus on different areas, such as hope for more time to spend with family, success in a new business venture, or finding a spouse. There is a diversity of hope in the medical realm as well. In many medical care settings, the hope is to restore patients to their prior state of health. In the NICU, the hope is to bring patients to a place of health that allows for growth and development. In other words, NICU care is framed around the hope for a future. Information about the infant's condition and prognosis is delivered every day by the care team in the context of hope for this future. Regardless of the information being delivered to the family, hope is at the center of how each family processes the daily medical information.

Many physicians struggle with the dissonance between delivering the bad news of a treatment failure or a new grim finding, and maintaining hope. Hope can become the elephant in the room in dire situations, an unspoken driving force for both the physician and family. Physicians in this situation may alter their delivery of information to "preserve hope."(10)(11). This most often occurs by the use of salvage statements (12) immediately following the bad news or by altering or withholding a prognosis. (13)

An example of using the salvage statement is as follows:

Physician: Your child was without oxygen for a long time, and her brain likely was damaged.
Family: Is it permanent?
Physician: Not necessarily, and the other organs are working well, which is encouraging.

An example of withholding prognosis:

Nurse: Have the parents been updated about their child's condition?
Physician: We talked about what cooling is, but we didn't talk about long-term outcome yet. I didn't want to take away their hope.

The medical team as a whole may view a family maintaining hope as evidence that they are "not getting it." (14) The physician may view hope as a sign of a lack of understanding or a form of denial. The physician may use repeated communications of medical information until there is evidence that the family has abandoned their hope for a cure.

> *Physician: How are you and your son today?*
>
> *Family: We are doing ok. We just spent most of the time praying. We are hoping for a miracle.*
>
> *Physician: So, unfortunately, I just don't think that's going to happen. The amount of time his brain was without oxygen was so long. Once that damage to the brain has occurred, the tissue cannot recover. Would it help to see the MRI again?*

Neither the strategy of avoiding prognosis, nor that of focusing on how the prognosis precludes hope is used with malicious intent. By not "taking away hope" the physician recognizes that hope is important to families dealing with serious illness. However, a survey of 194 families of children with cancer demonstrated that truthful delivery of prognostic information did not affect their hopefulness regardless of the content of the communication. (11) In fact, good communication of medical information *allows* for hope, (11)(12)(15) and builds trust between physician and family. Likewise, the care team that works to ensure a family "gets it" does not intend to increase their suffering. The team may want to avoid giving "false hope" so that the family can make appropriate decisions about goals of care (16) or perhaps simply to ensure that the family processes the difficult road ahead. (12) However, as Whitney et al state, "acceptance cannot be done to, or for, the patient; the patient must do it." (12)

Then what is to be done with hope? A common scenario is that physicians mistake hope as a singular entity (ie, hope is the cure). However, hope is not singular. It is complex, a grouping made up of many hopes. (12)(16) Of course the family is hoping for a cure. A neonatologist charged with the healing of critically ill newborns is hoping for a cure as well, even in the gravest of situations. But what else is the family hoping for? What are their other hopes? Asking a family what they are hoping for is an opportunity to hear about, and align with, their values. (14)(17)(18)

> *Physician: Given this new information from the MRI, I am wondering, what is it that you are hoping for?*
>
> *Family: We are hoping she will get better.*
>
> *Physician: It is obvious you love her very much. I am hoping for the same thing. What else are you hoping for?*

While this first hope may not be attainable, it can be validated. Asking about the family's other hopes allows the physician to begin to explore what makes up the entirety of the family's hopes. The family may list among their other hopes that their child be baptized, or spend time with extended family before she dies. They may hope for her not to suffer or feel pain. Unlike the primary hope (ie, a cure), these hopes are more likely to be achievable.

While many clinicians avoid discussing hope for many different reasons, hope is used similarly as the word "everything." A discussion about hope can be an opportunity to align with the family, gain trust, and better understand the family's values to jointly direct goals of care. Instead of avoiding the singular hope of a cure, neonatal clinicians should embrace the idea that families have multiple hopes for themselves and their child. Recognizing this idea should alleviate the anxiety and fear around discussing a family's hopes.

"WITHDRAWAL OF CARE"

> *A 5-day-old term male infant with severe hypoxic-ischemic encephalopathy was treated with whole body therapeutic hypothermia. He has just had a brain MRI. Clinically, he remains apneic on the ventilator and has near-continuous subclinical seizures despite maximal therapy. The MRI shows diffuse global ischemic damage. The family decides that they do not want him to suffer and discuss end-of-life care with the neonatologist. After the discussion, the neonatologist tells the charge nurse, "the family wants to hold him, and then we will withdraw care."*

The words that caregivers use with families must be thoughtful, empathetic, and personalized to that child and family. (15)(19)(20)(21) We suggest, however, that some phrases should be avoided all together. One such phrase is "withdrawal of care."

For parents, the decision to make a transition away from life-sustaining interventions to treatments focused on maximizing comfort can be emotionally stressful. (15)(20) The care team has the opportunity to guide and support them through this difficult transition. In the highly stressed, emotionally charged atmosphere that inevitably accompanies the death of an infant or child, families remember the specifics of the care for their dying child, including seemingly benign statements made by the medical team. (19)(20)(21) Medical team communication can be perceived as a helpful or detrimental aspect of end-of-life care by families. (17)(19) Clinicians should be sensitive to the potential to both support and inadvertently harm families with the content of their communications at the end of their infant's life.

One of the biggest fears at the end of life is fear of abandonment by the medical team. (20) Language such as the phrase "withdrawal of care" can be interpreted by families as a cessation of all medical care of the infant and all supportive care of the family at the time the endotracheal tube is removed. As a whole team, we may remove an endotracheal tube, stop artificial nutrition and hydration, and cease life-sustaining therapies. But we never *withdraw care*. (22) In fact, at the end of life, one could argue that the care is more intense, with special attention being paid to support the infant and family. (19)(20) Instead, language such as "redirection of care" or "foregoing artificial life-sustaining treatments" can be used to recognize that care consisting of medications for infant pain and dyspnea, and psychosocial support for the family will continue, while interventions such as mechanical ventilation and intravenous nutrition are discontinued. A seemingly minor change in words may have a profound change in meaning for the family.

CONCLUSION

Effective, compassionate communication is integral to providing high-quality care in the NICU. Certain phrases and ideas have significant weight for both physicians and families. Many of these are actually opportunities to have extremely fruitful conversations with families. The concepts of "everything" and "hope" can provide the opening for critical, nuanced conversations that will allow the family and care team to communicate about the family's true goals of care.

Medical teams should also be aware of the power that words have on the care that they provide. We need to be explicit in the words we use. Phrases such as "stopping care" and "withdraw care" signal a cessation of medical and psychosocial care and thus misrepresent both the intent and complexity of "redirecting the goals of care." If we are aware of the power of words in this context, it can be the foundation for building a culture of support and elevate the quality of care we provide to infants and their families.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the components of bereavement counseling prior to, during, and after the death of a newborn infant, including palliative care.

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1. A family is informed of a prenatal diagnosis of a complex congenital heart defect that is likely to be lethal within the first month after birth. The fetus is now at the 22nd week of gestation. With their first response to the news, the mother says, "Please do everything possible for our baby." What is the most appropriate way to respond to this statement?
    - A. Because the parents have full autonomy in decision-making for their child, a plan for full code and surgical repair should be made.
    - B. Although they have expressed their intent clearly, this is a circumstance in which the family should be directed toward therapeutic abortion as soon as possible.
    - C. The physician can use this statement as a starting point to uncover the family's values, hopes, and fears, and begin a conversation to inform goals of care.
    - D. An ethics committee consultation should be obtained before proceeding with any further discussion with the family.
    - E. While the physician should show empathy for the family's situation, the physician should only state the facts and not delve into the motivations behind the family's values or preferences.
2. A male infant who was born at 23 weeks' gestational age is now 1 day old and receiving high-frequency oscillatory ventilation in the NICU. The ventilator is set at high pressures and 100% oxygen, the infant is hypotensive, and there has been no urine output since birth. You are having a frank discussion with the family about the grim prognosis. The father states that he wants "everything" to be done for his son. While it can be challenging to read the meaning behind parents' statements in these situations, which of the following is the most reasonable interpretation of this statement and/or next appropriate step for care?
    - A. He has a clear idea of the situation and would like to proceed to full code, but the medical team can stop resuscitation if there is no heart rhythm for more than 10 minutes.
    - B. He is asking for the medical team to provide a list of possible therapies for which he will give full approval.
    - C. The family needs time to mourn and further discussion should be withheld until the parents reach out to the medical team again.
    - D. He may be making an emotional appeal for support in the context of hopes that he had harbored for the survival of his child.
    - E. An ethics committee consultation should be made to allow the medical team to make all decisions for the infant.
3. A male infant who has suffered from hypoxic-ischemic encephalopathy after placental abruption has undergone therapeutic hypothermia. Magnetic resonance imaging of the brain is performed after rewarming and shows abnormal T1 and T2 hyperintensity with restricted diffusion in multiple regions. Based on clinical criteria, the patient is considered to have severe neonatal encephalopathy. The mother has been in intensive care but has now recovered and has been receiving news about her son from the father. She is at the infant's bedside for the first time and there is a concern about sharing "bad news" with her. Which of the following principles of communication is relevant to this scenario?
    - A. Good communication of medical information allows for hope and builds trust between the physician and family.
    - B. Unless there is an imminent need for a clinical decision, information about patient status and prognosis should only be shared when parents ask for it.
    - C. If there is a mention of hope, the primary role of the physician is to make sure that the parents abandon their hope to match reality.
    - D. In times of stress, the topic of prognosis should not be discussed.
    - E. The best course of communication is to focus on the positives (the infant has good urine output and is starting to breathe on his own) and avoid mentioning any negative clinical issues.

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4. An infant born at 24 weeks' gestational age has had an eventful first 2 days after birth, requiring escalation of respiratory support, and is now receiving 100% fraction of inspired oxygen on high ventilator settings, with the need for inotropic support and multiple blood product transfusions. Head ultrasonography shows grade 4 intraventricular hemorrhage. In a meeting with the family, the father states, "We are hoping for a miracle. I hope that you can help her." The neonatologist responds, "I can tell that you care for her deeply. What are some of the things that you are hoping for her?" How does this response align or not with principles of clinician-family communication?
   - A. Although well-intended, this response is not appropriate because of the way it provides false hope for the family.
   - B. This type of statement from the father is not meant to be a question and should not be answered, because a positive response may be interpreted as validation of a religious belief.
   - C. This is an appropriate initial response, but from this point forward, the neonatologist should work toward making sure that the family accepts the certainty of a poor outcome.
   - D. Because hope is not a singular entity, it can be appropriate to elicit aspects of the family's other hopes to learn about and align with their values and gain their trust.
   - E. The word "hope" is a loaded term and should not be used by the clinical team.
5. An infant with complex congenital heart disease has undergone surgical repair but has had major complications including stroke and renal failure. It has become evident that the maximization of clinical therapy will not be able to save the infant and death is likely to occur within the next few days. Both the parents and clinical team have accepted this inevitable outcome. As discussions continue on the next steps for care, which of the following is the most appropriate term to use with the family and medical team to describe this stage of care?
   - A. Redirection of care.
   - B. Withdrawal of care.
   - C. Active shortening of dying process.
   - D. Withholding of care.
   - E. Limiting the amount of care.

Magnetic Anastomosis as a Minimally Invasive Treatment for Esophageal Atresia

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ABBREVIATIONS

EA	esophageal atresia
FDA	Food and Drug Administration
HDE	Humanitarian Device Exemption
HUD	Humanitarian Use Device
NG	nasogastric
SIRS	systemic inflammatory response syndrome
TEF	tracheoesophageal fistula
VACTERL	vertebral, anorectal, cardiac, tracheal, esophageal, renal, and limb anomalies
VATER	vertebral anomalies, anal atresia, tracheoesophageal fistula/esophageal atresia, and radial dysplasia

Education Gaps

1. Several surgical procedures have been described in the literature which lengthen and approximate the ends in long-gap esophageal atresia.
2. A new minimally invasive procedure approved for a US Food and Drug Administration Humanitarian Device Exemption has now emerged as a possible treatment option in place of, or in conjunction with, surgical repair for infants with esophageal atresia. This procedure uses magnets placed under fluoroscopic guidance to create an anastomosis between the stomach and esophagus.

Abstract

Esophageal atresia without fistula is a rare congenital abnormality for which treatment historically required a surgical repair. A new minimally invasive procedure with US Food and Drug Administration–approved Humanitarian Device Exemption has now emerged as a possible treatment option in place of, or in conjunction with, surgical repair for infants with esophageal atresia. This procedure uses magnets placed under fluoroscopic guidance to create an anastomosis between the stomach and the esophagus. In this article, we will review a new magnetic anastomosis catheter-based system, describing how the procedure is performed as well as the reported outcomes and potential complications of this approach. We will highlight a recent case of a patient who underwent the procedure.

Objectives After completing this article, readers should be able to:

1. Recognize common presentations of infants with esophageal atresia with or without tracheoesophageal fistula and techniques used to confirm the diagnosis.
2. Describe the key components of the magnetic anastomosis procedure.
3. Identify types of esophageal anomalies that preclude candidates from being eligible for the catheter-based magnetic anastomosis.

INTRODUCTION

The term esophageal atresia (EA) comprises a group of congenital abnormalities defined by discontinuity of the esophagus. EA may also involve communication with the trachea, known as *tracheoesophageal fistula* (TEF). (1) The principal problem in the repair of an EA is the need to establish an anastomosis between 2 structures that may be significantly spaced apart, such as in long-gap EA (defined as a gap >4 cm). The chief concern with a repair across a large gap is tension on the anastomosis leading to dehiscence, anastomotic leak, or inability to complete the procedure. Multiple options exist for lengthening and approximating the ends in long-gap EA such as myotomies, Gough flap, or the Foker technique. With primary surgical repair of even the shortest-gap EA, defined as ≤1 cm gap, anastomotic leak and stenosis at the site of surgical repair are potential complications. (2) A minimally invasive approach with a Food and Drug Administration (FDA)–approved Humanitarian Device Exemption (HDE) uses magnets placed under fluoroscopic guidance for either single or staged repair of EA. This is now a treatment option that has shown initial encouraging results in patients with an EA and a gap less than 4 cm. (3)

ESOPHAGEAL ATRESIA/TEF

EA with or without TEF is the most common congenital esophageal anomaly, with an incidence of approximately 1 in 3,500 births. (4) The embryology of normal human tracheoesophageal development remains poorly understood, and the pathogenesis of EA and TEF remains controversial. (5) The etiology of EA has yet to be elucidated, but has been linked to multiple genetic and environmental aberrations. (1) Prenatal ultrasonography may raise suspicion for EA when there is polyhydramnios with absent stomach bubble. (5) If not diagnosed prenatally, infants with EA/TEF will likely present soon after birth with excessive oral secretions despite frequent suctioning, feeding intolerance, and cyanotic or apneic episodes. When EA is suspected, the clinician should attempt to pass a radiopaque nasogastric (NG) tube into the stomach. In the absence of atresia, the NG tube will reach the stomach, but in affected newborns, resistance will be met before the tube can reach the stomach. EA is confirmed when chest radiography shows coiling of the NG tube in the neck or upper chest, when the tube is unable to pass the proximal esophageal pouch. (6) EA has been associated with several other congenital anomalies such as VATER. VATER is an acronym first coined in 1972 by Quan and Smith as the nongenetic, nonrandom association of vertebral anomalies, anal atresia, TEF/EA, and radial dysplasia. The acronym was later expanded to VACTERL to account for the cardiovascular, renal, and limb abnormalities that may also be present. (7)

PRESENTATION

A 28-week-gestation male monochorionic, diamniotic twin weighing 1,105 g was born via emergency cesarean delivery after premature rupture of membranes with active labor and breech malpresentation. The patient required intubation and surfactant in the delivery room for respiratory distress. EA was suspected when chest imaging demonstrated coiling of the NG tube within the esophagus. The infant was diagnosed as having TEF and EA. On postnatal day 3, the patient underwent fistula disconnection and gastrostomy tube placement. Three months later, a fluoroscopic contrast study demonstrated an esophageal gap measuring 6 mm between the proximal and distal ends of the esophagus. The patient's course was complicated by a patent ductus arteriosus requiring surgical ligation, bronchopulmonary dysplasia requiring tracheostomy placement for prolonged mechanical ventilation, and retinopathy of prematurity requiring bilateral laser ablation therapy. At 7 months of age, the patient was transferred to our facility after obtaining institutional review board approval to perform magnetic anastomosis with the neodymium-iron-boron catheter–mounted device with magnets; this procedure was FDA-approved as a Humanitarian Use Device (HUD) at that time.

The device (Fig 1) consists of 2 catheters, each containing a mounted neodymium-iron-boron magnet at the end. A magnetic gastrostomy catheter is placed in the distal pouch and includes a retention balloon as well as a gastric flush and feeding port. The catheter placed into the proximal pouch also includes an inner catheter with a magnet and an outer catheter with a suction port for the evacuation of saliva.

For the magnetic anastomosis procedure, the patient was transported to the operating room and placed in the supine position on the fluoroscopy table. The indwelling gastrostomy tube was removed and the 18F magnet-loaded gastrostomy catheter was placed in the distal esophageal pouch over a guide wire. The magnetic end of the catheter was placed as close to the distal esophageal pouch as possible. The guide wire was then removed, the gastric retention balloon was filled, and the external bolster secured against the skin. This fluoroscopic-guided technique was used to guarantee that the magnet was placed in the pouch and not

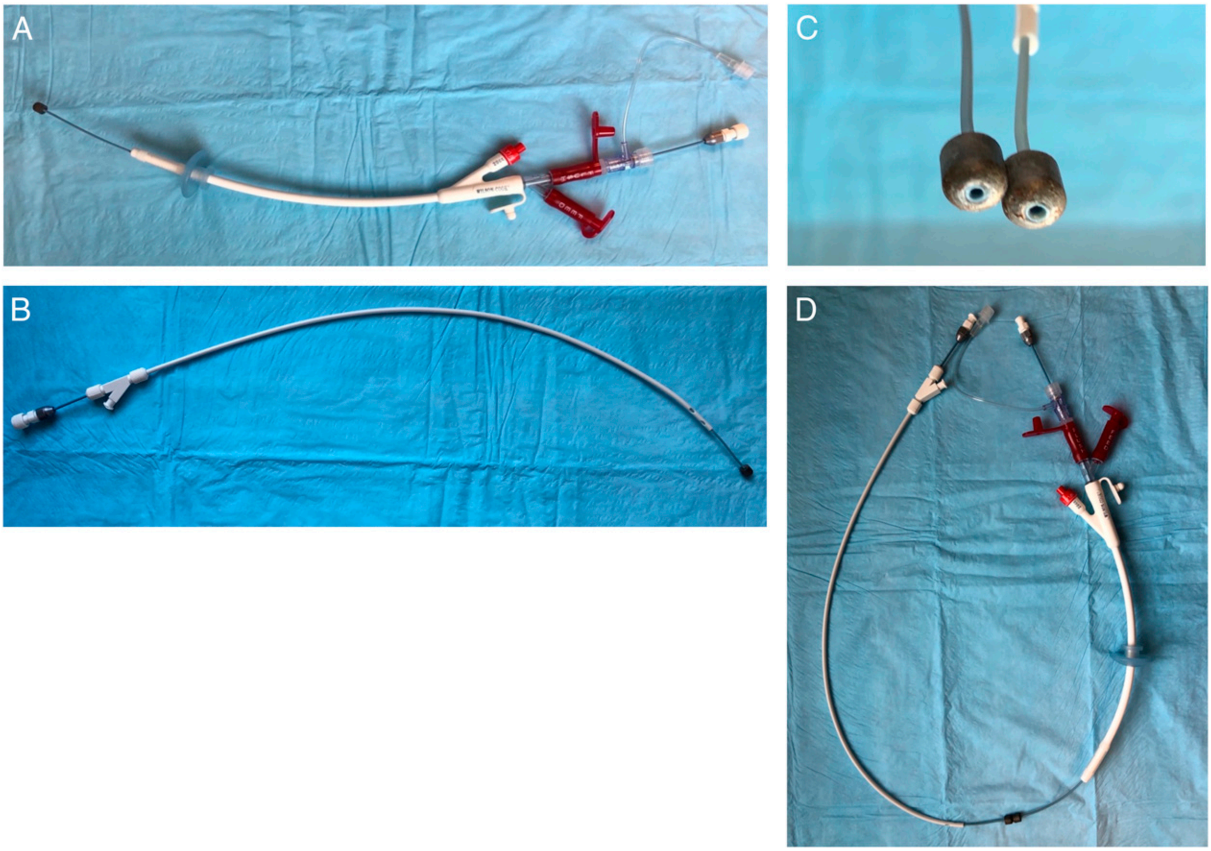

Figure 1. Image showing one type of catheter system. A. The lower device (gastrostomy tube). B. The tips of the magnets. C. The upper device (mouth piece). D. The 2 catheters with the magnets coupled.

the stomach fundus. The proximal magnetic catheter was then placed directly via the mouth and down the esophagus into the distal portion of the proximal esophageal pouch under fluoroscopic guidance. Magnetic coupling was observed almost immediately. A postprocedure chest radiograph was obtained to assess for evidence of esophageal perforation, such as cardiomediastinal widening or pneumomediastinum. The radiograph was reassuring, with magnets appearing in the appropriate position. The postprocedure fluoroscopic image demonstrating the initial orientation of the magnets is shown in Fig 2. The goal of the procedure is for the magnets to remain in place to form the compression anastomosis. To facilitate this, the upper catheter contains a suction lumen to aspirate oral secretions and the lower catheter contains a feeding gastrostomy channel to provide full enteral nutrition.

In the early morning of postprocedure day 3, the patient developed signs of infection with fever, elevated white blood cell count, and elevated C-reactive protein level. Cultures did not grow a pathogen, but the infant was treated for 7 days with vancomycin and cefepime and showed clinical improvement. Ten days after the procedure, the patient experienced a severe respiratory decompensation requiring sedation and pharmacologic paralysis.

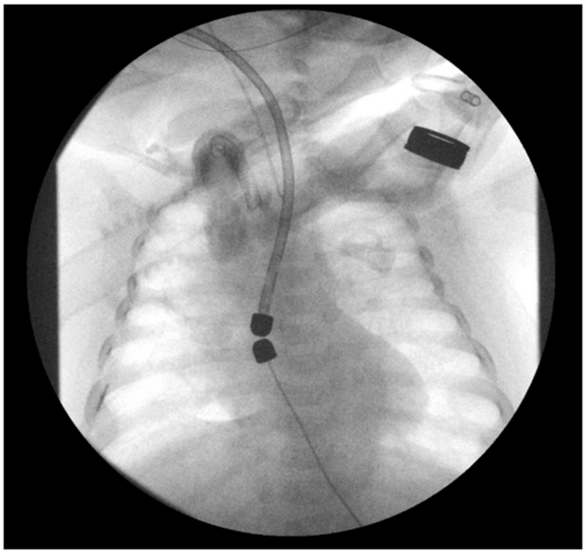

Figure 2. Immediate postprocedure fluoroscopic image demonstrating the initial position of magnets in appropriate orientation.

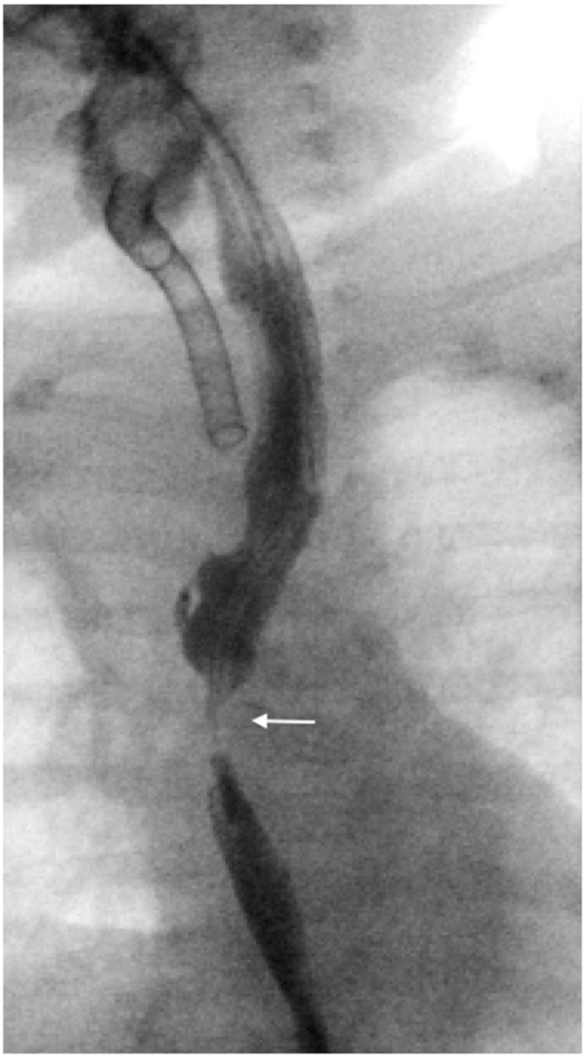

Figure 3. Postprocedural esophagram 2 weeks after magnet removal demonstrating esophageal stenosis (arrow) at the level of the anastomosis, but without evidence of contrast leak.

Because of the infant's clinically unstable condition, magnet removal was delayed until postprocedure day 13; however, luminal continuity was noted on day 10 after magnet placement.

For removal of the magnets, the patient was transported to the fluoroscopy suite and under fluoroscopic guidance, a stiff guide wire was advanced into the esophageal magnet end. The retention balloon on the magnetic gastrostomy catheter was deflated and both magnets were then gently pushed down from the oral end until they exited the gastrostomy site on the skin surface. An orogastric tube was then left in place after the magnetic catheters had been removed.

The patient remained nil per os for 2 weeks after magnet removal until reevaluation with an esophagram demonstrated anastomotic stenosis without evidence of a contrast leak (Fig 3).

Weekly esophageal dilating procedures were performed over 4 consecutive weeks to ensure an appropriate esophageal luminal diameter. The patient was subsequently transferred back to his home institution for ongoing intensive care.

DISCUSSION

Patients born with EA traditionally require surgical repair, sometimes consisting of multiple staged surgeries involving thoracotomies or thoracoscopies. The neodymium-iron-boron catheter-mounted magnetic device was FDA approved for an HDE in May 2017 as a minimally invasive alternative to surgical repair of EA. In this procedure, as described herein, magnets are placed under fluoroscopic guidance to establish magnetic anastomosis ("magnamosis"). This is particularly helpful in those patients who cannot undergo initial or repeat thoracotomy or thoracoscopy due to anatomic considerations or overall severity of illness.

Anastomosis by compression was first described in 1826 by Denans, who studied a device utilizing metal rings in an animal model. (8) In the 1970s, Hendren and Hale described clinical outcomes of magnet-induced growth in patients with EA and high-pouch imperforate anus. (9) Subsequently, multiple case reports demonstrated the use of magnets in creating magnetic compression anastomoses in different scenarios, such as gastroenteric anastomoses in malignant upper gastrointestinal obstructions, choledochoduodenostomy in benign common bile duct obstructions, among other gastrointestinal anastomoses. (9) When the magnets connect (ie, couple), the intervening tissue is compressed, becomes ischemic, and then sloughs centrally, while the outer anastomotic rim heals. In EA, magnetic anastomosis is achieved with the device described here after an average of 6 days (range, 2–12 days)(3)(9)(10) (M. Zaritzsky, unpublished data).

In patients with EA, magnetic anastomosis using the catheter-based system was first reported in 5 infants in Argentina. (10) Catheter-based magnetic anastomosis was also successful in patients with EA and proximal TEF, with the first clinical results published in 2016. (3) At the time of this writing, 13 infants have undergone the procedure in the United States and Canada. In all but 2 reported cases of EA, magnetic compression anastomosis was successfully achieved, but in most cases residual esophageal stenosis occurred, which required balloon dilation or other further interventions. (11) It remains unknown if the residual esophageal stenosis in part relates to the small size of the magnetic devices (10F catheter at the coupling surface);

however, patients who undergo surgical repair are also predisposed to having gastroesophageal reflux and recurrent esophageal strictures. (9) The frequency of esophageal stricture after catheter-based magnetic anastomosis observed to date suggests that a dilating regimen should be anticipated, and plans made to achieve the final age-appropriate caliber of the repaired esophagus.

Two types of patients with esophageal anomalies are not candidates for the catheter-based magnetic anastomosis. The first is patients with type E esophageal anomaly (ie, an H-type TEF), because the esophagus is already in continuity; the second is patients who have a long-gap atresia (defined as a gap length >4 cm between esophageal and gastric pouches). A gap greater than 4 cm exceeds the strength of the magnets and renders the catheter-based device ineffective. (11) However, patients with a gap greater than 4 cm can have esophageal stretching procedures to narrow the gap before magnetic anastomosis is used, as reported in 2 patients. (11)

The patient described herein developed systemic inflammatory response syndrome (SIRS) 3 days after the magnets were placed. This was believed to be an inflammatory response associated with the procedure, because no infectious etiology was identified. Therefore, the decision was made to allow the magnets to remain in place until anastomosis was achieved. A similar SIRS episode in a pediatric patient 48 hours after magnet placement has been described in the literature (9)(10); however, in that case, the magnets were prophylactically removed and replaced following antibiotic therapy and clinical improvement.

It has been suggested that tissue necrosis can induce an inflammatory or SIRS response, which has been demonstrated in animal models. (12) Cytokines, phagocytes, and host tissue damage–associated molecular patterns may be released by injured/necrotic cells, and can mediate a local and systemic inflammatory response in the absence of infection. (13)(14) It is believed that when the magnets connect, the compressed tissue undergoes necrosis, but it is unclear if the amount of tissue necrosis that occurs is enough to trigger a systemic inflammatory reaction. Further experience with this technique will help define the frequency with which a noninfectious SIRS response might be expected after the magnetic anastomosis procedure.

By the age of 30 months, the patient required 7 dilating regimens, the first occurring approximately 3 weeks after the magnets were removed. The last dilation took place at age 12 months, and the caliber of the esophagus was seen to be improving on subsequent follow-up examinations. Although the patient has been able to manage his secretions, he has an oral aversion and continues to remain gastrostomy tube–dependent.

CONCLUSION

The catheter-based magnamosis is a minimally invasive alternative to surgical repair. This technique may be used as a primary intervention or in combination with surgery in a staged repair of patients with EA both with and without TEF. The positive results in patients with EA highlight the potential for magnetic compression anastomosis to be used in other appropriate pediatric medical conditions. (3) Further investigation is necessary to explore the pathophysiology underlying the sepsislike response demonstrated in some patients after magnet placement, as well as the high rates of postprocedural esophageal stenosis.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the various types and diagnostic features of tracheoesophageal fistulae and esophageal atresias.
- Know the management and the complications of surgical repair of tracheoesophageal fistulae and esophageal atresias.

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1 Term Infant with Abdominal Distention and Refractory Hypertension

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AUTHOR DISCLOSURE Dr Ji and Ms Kudalmana have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male neonate is born at an estimated 37 3/7 weeks' gestation via emergent repeat cesarean section to a 25-year-old gravida 6, para 5 Hispanic mother. Pregnancy, labor, and delivery complications include oligohydramnios, decreased fetal movement, non-reassuring fetal status with fetal tachycardia and minimal variability, and meconium-stained amniotic fluid on delivery. The neonate is "stunned" on presentation with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively, with a birthweight of 2,929 g. He was admitted to the NICU for further evaluation and management of abdominal distention.

On examination, the neonate is found to have moderate abdominal distention and firmness, hypoactive bowel sounds, brown fluid produced from oral suctioning, similar brown fluid produced from urethral opening, patent anus, hypoplastic nails, and a short hallux of the left foot. The remainder of the examination findings are unremarkable. Kidneys, ureters, and bladder (KUB) are examined because of the abdominal distention, and showed a gasless abdomen with a small gastric bubble. Abdominal ultrasonography is then conducted because of an inability to view the liver and spleen, which showed findings of moderate ascites. The ascites with the combination of pulmonary edema on chest radiography gave rise to a concern for hydrops fetalis (Fig).

DISCUSSION

Diagnosis

Further concern for malrotation and volvulus with continued abdominal distention and progressive bluish hue on the abdomen led to an upper gastrointestinal study with small bowel follow-through, the result of which was normal. Exploratory laparotomy was conducted on day 2 after birth, which uncovered a frank perforation at the distal ileum. An 8-cm small-bowel resection with ileostomy and mucous fistula was performed. After 5 days of enteral feeds, the neonate showed resistance and disinterest to feeds with recurrent emesis. Repeat abdominal ultrasonogram, head ultrasonogram, and KUB radiograph were all normal. The neonate started showing interest in feeds after making a transition to an amino acid–based infant formula. On day 50, the neonate underwent bowel reanastomosis with gradual advancement of feeds to full feeds by day 62.

The neonate was noted to have intermittent periods of hypertension in the setting of feeding intolerance on day 13 after birth. The incidence of neonatal hypertension ranges from 0.2% to 3% with the differential including renovascular (thromboembolism, renal artery stenosis, midaortic coarctation, compression of

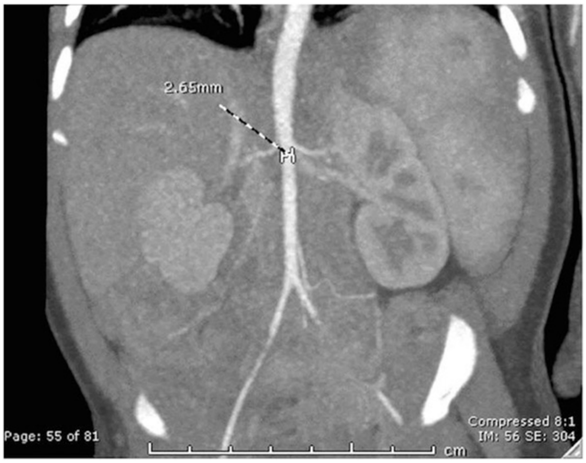

Figure. Computed tomography angiography showing abdominal aortic narrowing.

renal artery, idiopathic arterial calcification, congenital and acquired causes), pulmonary (bronchopulmonary dysplasia, pneumothorax), cardiac (thoracic aortic coarctation), endocrine (congenital adrenal hyperplasia, hyperaldosteronism, hyperthyroidism), medications, neoplasia (Wilms tumor, neuroblastoma, pheochromocytoma, mesoblastic nephroma), neurologic (intracranial hypertension, pain, subdural hematoma), and miscellaneous (adrenal hemorrhage, hypercalcemia, nephrocalcinosis, total parenteral nutrition) causes. (1) Echocardiography was conducted to rule out congenital heart diseases, with the results showing normal cardiac function. After negative urinalysis findings and normal renal ultrasound scan, nephrology recommended starting isradipine with gradual increase in dose for a blood pressure goal of less than 100/60 mm Hg. He was given intermittently trials of hydralazine on day 50 without effect. Isradipine was then restarted without improvement, resulting in a medication switch to captopril on day 53. Repeat renal ultrasonography on day 66 showed normal renal morphology with slightly elevated flow velocity at the origin of the left renal artery. Peripheral velocities are symmetric, with the right kidney and resistive indices being within normal limits. As part of the hypertension workup, renin, aldosterone, and cortisol levels were checked, results of which were within normal limits. Chromosome microarray analysis results were negative as well.

Given the history of intestinal perforation and refractory hypertension, the nephrologist recommended computed tomography angiography, which revealed the diagnosis of midaortic syndrome. Amlodipine was then started with greater control of hypertension, leading to discontinuation of captopril on day 81.

The neonate was discharged from the hospital on day 84 with labetalol and amlodipine, with well-controlled blood pressure. He was closely followed by the nephrology and surgery teams.

The Condition

Midaortic syndrome is a rare condition found in children and young adults that is characterized by segmental narrowing of the abdominal aorta with involvement of the major branches. (2)(3)(4) It is most often congenital because of irregularity with the fusion and maturation of the embryonic dorsal aortas during development, but acquired causes include neurofibromatosis, fibromuscular dysplasia, Williams syndrome, retroperitoneal fibrosis, giant cell arteritis, mucopolysaccharidosis, and other in utero insults to the developing aorta. (3)(5) It can present with fetal findings of hydrops fetalis, growth restriction, and polyhydramnios. (4)

Midaortic syndrome has a diverse presentation that includes refractory hypertension, failure to thrive, abdominal bruit, diminished arterial pulses of the lower extremities, congestive heart failure, cardiomyopathy, and renal dysfunction. (4) Symptoms are usually secondary to hypertension, but claudication and intestinal ischemia may be present. (2) This is seen in the current case, in which the patient presented with intestinal perforation due to ischemia as the primary problem.

Hypertension is usually difficult to control with chronic malignant hypertension being the cause of most of the complications associated with this syndrome. The preferred diagnostic test for midaortic syndrome is angiography of the descending and abdominal aorta. (3)(4) The goal of treatment is to normalize the patient's blood pressure to avoid complications secondary to hypertension, preserve renal function, and resolve claudication by using approaches that include pharmacotherapy, endovascular treatment, and surgical intervention. (3)(5)(6) Surgical therapy has been shown to be curative in most patients and has become the treatment of choice, (3)(5) but antihypertensive medication can be used as a bridge to surgery, especially for neonates.

Lessons for the Clinician

- Midaortic syndrome should be in the differential diagnosis in pediatric cases of intestinal ischemia with perforation and refractory hypertension.
- The gold standard for diagnosis of midaortic syndrome is angiography of the aorta with either computed tomography or magnetic resonance imaging.
- Surgical therapy has been shown to be the treatment of choice, but antihypertensive pharmacotherapy can be used to bridge surgery, especially for neonates.

ACKNOWLEDGMENTS

We thank Dr Kartik Pillutla and Dr David Simon, pediatric nephrologists at Dell Children's Medical Center of Central Texas, and Dr Eugene Tong, diagnostic radiologist, for assistance with diagnosis and patient management.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Formulate a differential diagnosis for an infant with systemic hypertension in early infancy.

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2 Coexisting Cystic Lesions of Lung in a Term Neonate: A Management Dilemma

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AUTHOR DISCLOSURE Drs Raut, Aakriti Soni, Badatya, Saluja, Modi, and Arun Soni have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term, 38-week-gestation, small-for–gestational age female infant weighing 2,135 g is delivered vaginally by a primigravida woman with an antenatal history of deranged Doppler flows. Resuscitation is not required at birth because the infant has normal Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. Prenatal ultrasonography reports the presence of congenital pulmonary airway malformation (CPAM) on the left side, which regressed after steroid treatment in the third trimester. Delivery room postnatal examination suggests that the heart sounds are prominent on the right side of the precordium with the infant maintaining target oxygen saturation on room air with no signs of respiratory distress. She is admitted to the NICU for observation and further evaluation of mediastinal shift.

CASE PROGRESSION

In the NICU, chest radiography reveals hyperinflated left lung with shifting of mediastinum to the right side (Fig 1). Computed tomographic (CT) imaging reveals left lower lobe CPAM with a posterior mediastinal cyst compressing the left main bronchus (Fig 2). Echocardiography and ultrasonography of the abdomen and cranium are performed to rule out other associated congenital anomalies, and are found to be normal. At 20 hours after delivery, she develops mild respiratory distress but does not require any respiratory support. Forty-eight hours after admission, the infant undergoes bronchoscopy to locate the

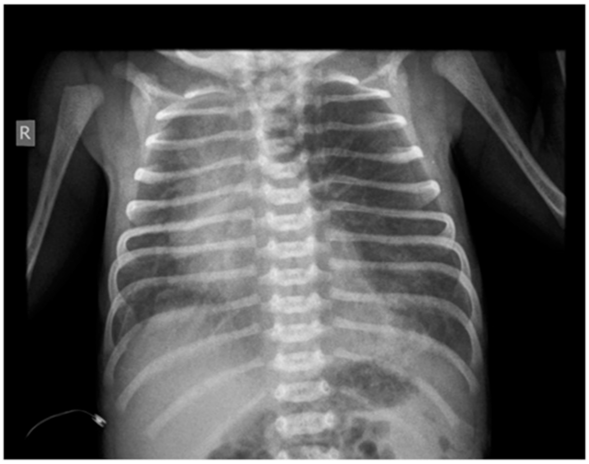

Figure 1. Chest radiograph showing hyperinflation of left lung with mediastinal shift to the right.

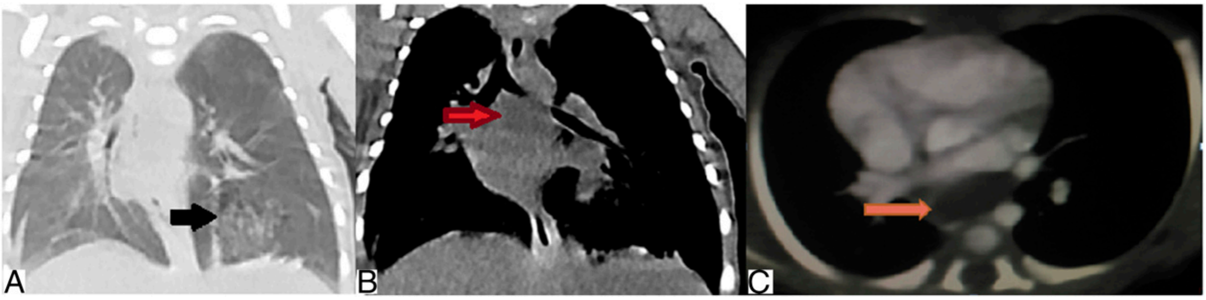

Figure 2. A–C. Computed tomography scan showing the presence of congenital pulmonary airway malformation (black arrow) and posterior mediastinal cyst (red arrow) with mediastinal shift.

site of airway obstruction, which reveals the presence of a bluish mass compressing the left main bronchus (Fig 3). This leads us to suspect a hemangioma or vascular malformation compressing the bronchus. However, CT pulmonary angiography rules out the presence of any such vascular malformation. The possibilities are thus narrowed down to the presence of a bronchogenic cyst as the infant continues to have mild respiratory distress with hyperinflated left lung and mediastinal shift to the right. Expert opinions of pediatric and cardiothoracic vascular surgeons are therefore sought and accordingly the infant undergoes surgical exploration. The consensus of the team is to perform a resection of the cystic lesion compressing the left bronchus, because it is believed that simultaneous resection of both cysts (CPAM and bronchogenic cyst) may put the infant under too much stress. Possibly the symptoms most likely to be seen are due to the compression effect of the bronchogenic rather than regressing CPAM. On the fourth day after delivery, after counseling the parents and obtaining their consent, the surgical team proceeds with a left thoracotomy, and intraoperative findings show an intramural cyst near carina, compressing the left bronchus. Because the cyst and bronchus share a common muscular wall, the cyst is excised, saving the muscle over the bronchus. Biopsy of the excised cyst shows features similar to those of the foregut and it is lined by pseudostratified ciliated columnar epithelium, which confirms the diagnosis of bronchogenic cyst. The infant continues to receive mechanical ventilation after surgery. However, on the second postoperative day, she undergoes extubation but does not tolerate it and develops stridor with severe respiratory distress, thereby needing re-intubation. A repeat flexible bronchoscopy is undertaken, which reveals subglottic edema, for which she is treated with systemic steroids and epinephrine nebulization. After this, she undergoes successful extubation on the second day of steroid therapy. The infant is now being discharged on day 15 after birth. The potential complications of CPAM, such as repeated chest infections, pneumothorax, and malignant potential, including their danger signs, have been explained to the infant's caregivers. A follow-up plan is made with regular assessment of growth monitoring and plan for an elective resection of the lower lobe at 6 months of age or earlier if required.

DISCUSSION

Incidence of congenital cystic lesions of lung is 1 in 25,000 to 35,000 live births. (1) CPAM is often described as a hamartomatous lesion because of abnormal development of the tracheobronchial tree. It develops during the pseudoglandular phase (7–17 weeks) of fetal lung development. Depending on the site of origin and histopathology, it is classified (Table 1) into 5 types. (2) Another classification proposed (Table 2) is based on antenatal ultrasonography. (3) This is useful in guiding the clinician to manage the antenatally diagnosed cases. (4) The 2 most important features for its diagnosis are 1) its connection to the tracheobronchial tree, and 2) vascular blood supply from the pulmonary circulation.

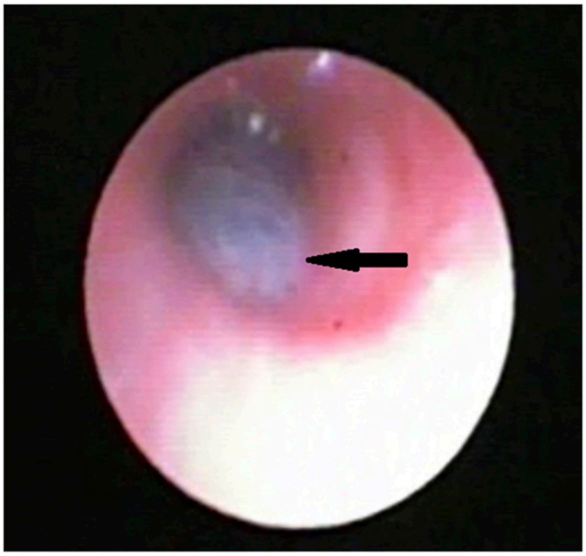

Figure 3. Bronchoscopy image showing extraluminal bluish mass (black arrow) on left main bronchus.

TABLE 1. **Classification of Congenital Pulmonary Airway Malformation Based on Site of Origin From Tracheobronchial Tree as Described by Stocker et al (2)**

TYPE	SITE OF ORIGIN
Type 0	Trachea
Type 1	Distal bronchi/proximal bronchiole
Type 2	Bronchioles, up to terminal bronchiole
Type 3	Alveolar duct/proximal acini
Type 4	Distal acini

Bronchogenic cyst arises as an abnormal bud from the primitive foregut. Depending on its timing of separation from the foregut, it may form an extrapulmonary cyst by migrating into the mediastinum if separated early, or alternatively, it forms an intrapulmonary bronchogenic cyst when separated late. Antenatally it can be diagnosed with ultrasonography wherein it appears as an anechoic, unilocular, intrathoracic cyst. Such antenatal diagnosis of cysts helps in their management and prognosis, because depending on their size, they may compress the lung or heart parenchyma, leading to pulmonary hypoplasia or hydrops, respectively. (1) Most patients remain asymptomatic after birth in case of small cysts. Coexistence of CPAM and bronchogenic cyst is very rare and unusual, (5) and patients may be symptomatic with either. In our case, despite the coexistence of CPAM and bronchogenic cyst, antenatal ultrasonography and fetal magnetic resonance imaging missed the bronchogenic cyst. Although CPAM was reported to be regressing, postnatal CT scan diagnosed the presence of both these cysts. Looking at the small size of CPAM, it appears that the hyperinflated left lung and compressed left main bronchus was caused by the bronchogenic cyst, resulting in mediastinal shift and respiratory distress in the infant described herein. Sometimes it may be difficult to differentiate CPAM types 0 and 1 from bronchogenic cyst. The differentiating points (Table 3), however, help in identifying the exact nature of the cyst.

TABLE 2. **Classification of Congenital Pulmonary Airway Malformation Based on Antenatal Ultrasonography Proposed by Adzick et al (3)**

TYPE	SIZE	APPEARANCE	PROGNOSIS
Macrocystic	>5 mm	Anechoic surrounded by hyperechogenic lung	Grows slowly Has a favorable prognosis
Microcystic	<5 mm	Homogenous solid mass, hyperechoic as compared to lung parenchyma	Larger in size and grow rapidly, often associated with mediastinal shift, pulmonary hypoplasia, polyhydramnious and hydrops Has a poor prognosis

TABLE 3. **Differentiation Between Congenital Pulmonary Airway Malformation (CPAM) and Bronchogenic Cysts**

CPAM	BRONCHOGENIC CYST
Usually air filled unless infected	Usually mucous filled unless infected
Cyst wall is thinner	Cyst wall is thicker
Surrounded by island of cartilage only	Surrounded by cartilage, smooth muscle, elastic tissue, mucous glands

Prognosis of cystic lung lesions depends on histopathology of the lesion, other associated congenital anomalies, presence or absence of hydrops, signs of cardiovascular compromise, and pulmonary hypoplasia due to mass effect. Survival to delivery is reported in 95% of cases of CPAM. In fetuses that do not develop hydrops, postnatal survival has been reported to be nearly 100%. In fetuses with hydrops that undergo prenatal intervention, survival has been reported at a mean of 80%, with rates up to 100% among those treated with thoracocentesis. Neonatal survival was 69%. (6) Postnatal management depends on whether the infant is symptomatic. If symptomatic, surgical intervention is definitive after stabilization. However, in asymptomatic cases, elective resection is safe and prevents the risk of symptom development, which may result in a more complicated surgery and recovery. (7)

Lessons for the Clinician

- Although rare, different types of cystic lung disease can be present together.
- It is very difficult for the clinician to make out which lesion is primarily responsible for the symptoms. Proper clinical assessment and investigations may help the

clinicians and surgeons to make a rational decision because multiple surgeries at the same time may not be tolerated by the infant.

- Although the infant may remain asymptomatic, surgical excision of congenital pulmonary airway malformation is necessary between 6 months and 1 year of age because of the future risk of recurrent chest infection, pneumothorax, and malignancy.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the appropriate management for an infant with congenital malformations of the lung, including congenital pulmonary lymphangiectasia, and the cystic lung diseases, such as congenital lobar emphysema, cystic adenomatoid malformation, and mediastinal tumors.

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3 Early Severe Jaundice in a Term Infant

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PRESENTATION

An appropriate-for–gestational age (AGA) African American female infant is born at term via elective, repeat cesarean section at 39 weeks' gestation to a gravida 2, para 2 woman. The mother's pregnancy had been complicated only by gestational hypertension, and maternal antenatal testing results were unremarkable. Maternal blood type is O positive with a negative antibody screen during pregnancy. Meconium fluid is noted at delivery; however, the infant is vigorous with a strong cry and requires only routine resuscitation with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. After resuscitation, the infant makes a transition to routine couplet care with an anticipated 48-hour stay.

A cord blood sample is sent for blood type and direct antiglobulin test (DAT) per hospital protocol secondary to maternal blood type finding of B-negative type with a negative DAT result. Her first 24 hours are uneventful with direct breastfeeding every 2 to 3 hours, 2 documented voids, 3 stools, and minimal weight loss. All documented vital signs and examination results are normal for a term newborn. At 24 hours after birth, a transcutaneous bilirubin test is attempted per standard newborn care plan, with the resulting value too high to detect. Serum total and direct bilirubin concentrations are found to be 21.7 mg/dL (360 μmol/L) and 0.6 mg/dL (10 μmol/L), respectively. The infant is transported directly to the NICU for continued management and preparation for possible exchange transfusion.

DIFFERENTIAL DIAGNOSIS

With any case of hyperbilirubinemia, especially with early-onset or rapidly increasing levels, it is important to keep a broad differential to avoid missing benign versus more severe causes of jaundice. Categorizing by time of onset into 3 categories can be useful in establishing a differential diagnosis. These categories are based on newborn age: less than 24 hours after birth, between 24 and 72 hours after birth, and beyond 72 hours after birth. (1)(2)

Neonatal jaundice or hyperbilirubinemia in the first 24 hours is pathologic and should prompt immediate evaluation by the medical team. A thorough physical examination of the patient and review of maternal medical records, including blood type, will help direct appropriate laboratory tests and medical management. Sepsis and hemolytic disease of the newborn, as well as glucose-6-phosphate dehydrogenase (G6PD) deficiency are a few of the causes of early-onset neonatal jaundice (Table).

TABLE. **Time to Onset of Pathologic Indirect Hyperbilirubinemia**

TIME AFTER BIRTH, H	CAUSES OF HYPERBILIRUBINEMIA
<24	Sepsis, hemolytic disease of the newborn, glucose-6-phosphate dehydrogenase deficiency
24–72	Sepsis, physiologic, polycythemia, cephalohematoma, increased enterohepatic circulation
>72	Sepsis, breast milk jaundice, metabolic disorders, extrahepatic biliary atresia

CLINICAL COURSE

Laboratory evaluation, including complete blood cell count (CBC), reticulocyte count, serum glucose, blood culture, blood gas, and repeat serum total bilirubin were sent upon admission, and the infant was given empiric antibiotics. Triple phototherapy, including a phototherapy blanket and 2 banks of lights, was initiated. A single 10-mL/kg bolus of normal saline (0.9%) was given and the infant was placed on maintenance intravenous fluids at a total fluid goal of 80 mL/kg per day. Serial neurologic examination findings remained unremarkable, and the patient showed no signs of lethargy, hypertonia, arching, retrocollis, or temperature instability. Immediate recheck of the total serum bilirubin after fluid administration showed a decrease to 21 mg/dL and a hematocrit value noted in free-flowing venous blood gas sample was 35%. Initial attempts to obtain a CBC and reticulocyte count were rejected because the increased bilirubin interfered with the laboratory's ability to interpret the results. While preparing to receive a double-volume exchange transfusion, high-intensity phototherapy was continued and a repeat serum total bilirubin 2 hours later showed a decrease to 18.8 mg/dL (321 μmol/L). An umbilical line was placed in consideration for potential exchange transfusion, which was ultimately deferred.

The first CBC result showed a hemoglobin of 11.7 g/dL (117 g/L), hematocrit of 35%, platelet count of $95\times10^3/\mu L$ (95×10^9/L), and a reticulocyte count of 40.8% (Fig 1). Total serum albumin was 3.4 g/dL (34 g/L) with an albumin-bilirubin ratio of 7.5 mg/g. Despite the initial negative result seen in the cord blood sample, the type and screen were repeated in the infant because of the clinical suspicion of antibody-mediated destruction from ABO incompatibility. The infant sample resulted in a blood type of B negative with a strong anti-B antibody. Because of the immune-mediated process, evidence of brisk hemolysis with high reticulocyte count, and significant hyperbilirubinemia, the decision was made to treat with 0.5 g/kg of intravenous immunoglobulin. Over the next several days, the infant's serum bilirubin reached a plateau near 14 to 15 mg/dL (240–257 μmol/L). After 7 days of phototherapy, the patient was discharged with a bilirubin of 11.8 mg/dL (202 μmol/L; Fig 2) and hemoglobin of 9 g/dL (90 g/L). An expedited newborn screen returned with a presumptive positive result for G6PD A-negative genotype. Subsequent testing weeks later revealed Gilbert disease, which is not normally associated with significant neonatal hyperbilirubinemia, but when combined with G6PD, causes a significant rise in unconjugated bilirubin levels in the neonate.

THE CONDITION

Bilirubin is produced by the breakdown of red blood cells (RBC) and the catabolism of heme by the reticuloendothelial system. In its unconjugated state, bilirubin is released into the circulation where it binds to albumin and is transported to the liver. Once it reaches the liver, this bilirubin-albumin complex is transported into the hepatocyte where it combines enzymatically with glucuronic acid in a reaction catalyzed by uridine diphosphate-glucuronosyl transferase (UGT1A1). Because of the decreased functioning of this enzyme in neonates, increased RBC turnover, and increased enterohepatic circulation, jaundice is seen to some extent in nearly all newborns. In most cases, transient jaundice is a benign condition and does not require treatment. However, in some cases, bilirubin rises to levels sufficient enough to cross the blood-brain barrier and deposit in the basal ganglia, causing acute and chronic bilirubin encephalopathy. This pathologic staining of the brain is called *kernicterus*, and although rare, remains a completely preventable cause of cerebral palsy, because high levels of bilirubin can affect the developing nervous system. While most hyperbilirubinemia is transient and treated easily with phototherapy, certain conditions may predispose a neonate to rapid increase in bilirubin that may require other therapies, including, but not limited to, pharmacologic treatment with agents such as phenobarbital or ursodeoxycholic acid or exchange transfusion. (3)

ABO Incompatibility

In the case of ABO incompatibility, a DAT should be performed to identify potential hemolytic disease of the

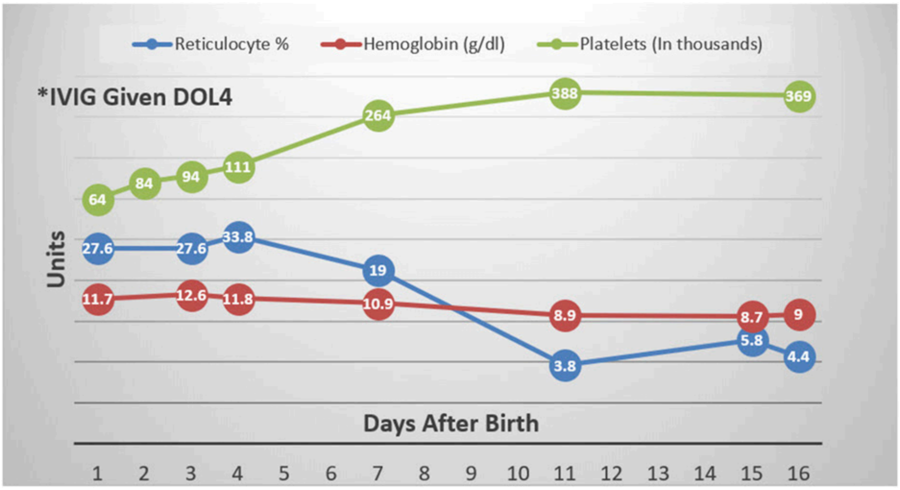

Figure 1. Trends seen in hemoglobin, platelets, and reticulocyte counts in the patient over the first 16 days after birth.

newborn (HDFN). However, an initial negative test result in the setting of increased clinical suspicion may prompt repeat laboratory testing as in the case described here. HDFN is caused by destruction of RBCs in the neonate because of maternal immunoglobulin G antibodies. Alloimmune HDFN can involve minor and major blood group incompatibilities, but usually involves the major blood groups including groups of Rhesus D (Rh), A, and B. In affected neonates, the clinical course can range from self-limited mild disease to life-threatening anemia. In most neonates, the first sign of disease is jaundice within the first 24 hours after birth. Patients with ABO incompatibility generally have a milder course and less severe disease compared with the Rh D incompatibility because of the presence of A and B antigens on other hematopoietic cells. (4)(5) African Americans with ABO incompatibility and DAT positivity may be at risk for severe hyperbilirubinemia associated with hemolytic disease. (6)(7)

Thrombocytopenia and ABO Incompatibility

Severe cases of HDFN are associated with thrombocytopenia likely related to consumption with hypersplenism and increased RBC production limiting marrow space. A and B blood group antigens are weakly expressed on platelets, but approximately 1% of the population will strongly express antigens on their platelets. In cases of ABO incompatibility there may be a component of

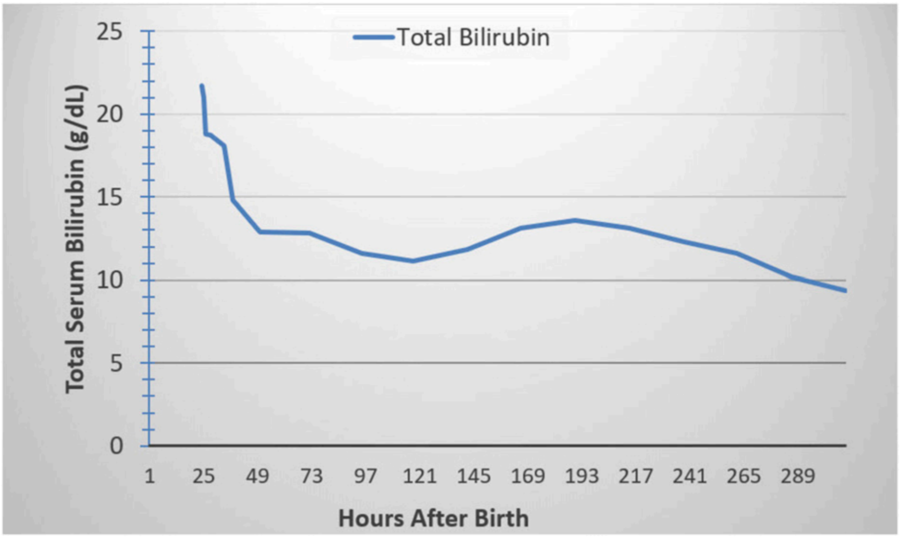

Figure 2. Trends seen in total bilirubin concentrations in the first 2 weeks after birth.

alloimmune destruction from the blood group–specific antibody. In such cases, treatment with intravenous immunoglobulin is therapeutic in both destroying RBCs and preventing severe thrombocytopenia. (8)

Glucose-6-Phosphate Dehydrogenase Deficiency

G6PD is the most common enzymatic disorder of RBC. It is a genetic disorder inherited in an X-linked fashion with wide variance in clinical expression. G6PD catalyzes the initial step in the hexose monophosphate shunt (HMP) by oxidizing the glucose-6-phosphate to 6-phosphogluconolactone to reduce nicotinamide adenine dinucleotide phosphate (NADP) to NADPH. The HMP shunt is the only source of NADPH in RBCs and prevents accumulation of superoxide radicals that can lead to hemolysis. Newborns with G6PD deficiency have a higher incidence of jaundice. Although the peak levels of hyperbilirubinemia occur at 2 to 3 days, the initial signs may be present early on. Kaplan et al showed that in G6PD alone there is a 9.7% rate of hyperbilirubinemia. G6PD is inherited in an X-linked recessive pattern. This results in pathology in affected males and perpetuation of carrier states in females. However, if a carrier/affected woman and an affected man conceive a daughter, she has a 100% chance of inheritance if the mother is affected and a 50% chance if the mother is only a carrier. (9)(10)

G6PD and Gilbert

Patients with Gilbert syndrome have decreased bilirubin conjugation because of a mutation in the bilirubin-UGT (*UGT1A1*) gene. *UGT1A1* conjugates bilirubin to glucuronic acid, converting the bilirubin into a water-soluble form that is readily excreted in bile. This defect causes a decrease in excretion and a subsequent increase in serum bilirubin levels. This is usually not clinically significant in the newborn, but in patients with G6PD and Gilbert UDPGT1 genotype, the incidence of hyperbilirubinemia increases to 31.6% in the heterozygous mutation and 50% in the homozygous mutation. (11) In our case, a screening for Gilbert was performed because of the disproportionately high level of bilirubinemia and clinical suspicion.

Lessons for the Clinician

- Neonatal hyperbilirubinemia, while common, requires consideration of a broad differential diagnosis, especially if it has a severe early onset (first 24 hours after birth).
- Severe jaundice that occurs in the first 24 hours after birth should be treated as pathologic. The differential diagnosis should include sepsis, hemolytic disease of the newborn, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- G6PD deficiency typically has an X-linked inheritance primarily affecting males; however, there are several inheritance patterns that can affect females.
- G6PD in conjunction with Gilbert *UDPGT1* genotype has a 3- to 5-fold increased risk of hyperbilirubinemia.
- Neonatal alloimmune thrombocytopenia is a platelet issue but can be precipitated by high AB antigen expression and ABO incompatibility. Double-volume exchange transfusion can rapidly decrease the circulating bilirubin level, but has potential for significant morbidity. Other options in the absence of neurologic signs of bilirubin encephalopathy are intravenous immunoglobulin G, fluid resuscitation, and aggressive phototherapy.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the differential diagnosis and evaluation of infants with indirect hyperbilirubinemia.

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3 Vacuum-Assisted Deliveries, 3 Bad Outcomes

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AUTHOR DISCLOSURE Dr Sims has disclosed that she has been compensated for reviewing records and providing testimony in some of the cases highlighted in Legal Briefs. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

CASE 1

A 39 2/7–week gestational age female infant with a birthweight of 2,995 g was born to a 31-year-old gravida 3 para 2 woman with an unremarkable pregnancy. Membranes ruptured spontaneously 19 hours before delivery with clear fluid. Because labor was not progressing, oxytocin was used to "expedite" the process. The fetus was initially occiput transverse, then occiput posterior. The obstetrician applied vacuum on the fetal scalp twice, but no descent was recorded. It was unclear what station the fetus was in when the vacuum was applied because of lack of documentation. ***The obstetrician retained by the plaintiff was critical of the treating obstetrician for not documenting the station of the fetus and repeating the vacuum because no descent was found after the first pull. He stated that without descent, reapplication of the vacuum is below standard.*** The obstetrician requested Simpson forceps after the failed vacuum. ***The treating nurse, in her deposition, admitted that it was against hospital policy to use forceps after a failed vacuum and stated that she questioned the obstetrician but that he ignored her. The plaintiff obstetrical nurse said that the nurse should have refused to bring the forceps and should have called her supervisor.*** The fetal heart rate monitoring tracings were largely unreadable, even when an internal monitor was placed 2 hours before delivery. ***The plaintiff obstetrician was critical of this and said that the obstetrical team needed to ensure adequate monitoring.*** The forceps were applied and considered "partially effective," as documented by the treating obstetrician, but the vacuum was reapplied. ***The plaintiff obstetrician was highly critical of using forceps after a failed vacuum attempt as well as the reapplication of the vacuum. The treating nurse said that she was uncomfortable with this process and tried to communicate this to the obstetrician. The treating obstetrician said he made a judgment call and it was a good one.***

A female infant was delivered and was given continuous positive airway pressure (CPAP) with supplemental oxygen for respiratory distress and cyanosis. The Apgar scores were 4 and 8 at 1 and 5 minutes, respectively. The infant's birthweight was 2,995 g (∼30th percentile), the length was 55 cm (99th percentile), and the head circumference was 33 cm (∼20th percentile). She was pale and her head, face, right eye, and scalp were bruised and edematous, with some abrasions and the scalp was boggy. Her right eye had ecchymosis of the upper and lower lids. The infant's respiratory distress worsened, and a pneumothorax was discovered on the initial chest radiograph, which was treated with needle aspiration. A transport team arrived shortly after birth and brought the infant to a tertiary medical center. The blood pressure remained stable and the infant did not require intubation. The infant's first complete blood cell count was unremarkable except for a hematocrit of 37%. A second hematocrit 9 hours later showed a value of 28%. The infant was given a diagnosis of subgaleal hemorrhage, cephalohematoma, and caput succedaneum. Two cranial ultrasound scans showed a hypoechoic collection above the scalp that crossed the coronal suture line, which was consistent with a subgaleal hemorrhage and a 1.7×1.1–cm hypoechoic lesion in the left middle cerebral hemisphere. ***The plaintiff neonatologist was critical that computed tomography (CT) or magnetic resonance imaging (MRI) should have been performed at least by day 4 because the infant was stable and the massive swelling on the scalp did not lessen.*** The infant was discharged a week after birth, feeding well and appearing intact except for the dramatic skull findings. Her head circumference was 3 cm larger than at birth. During a follow-up visit at age 3 months, the mother shared her concern that the scalp swelling had not lessened, but in fact was increasing. An MRI was immediately performed and showed extrusion of the brain with secondary leptomeningeal cyst formation. The records show that the infant's brain herniated through the dura as a result of skull fractures, and portions of it were strangled. At age 3 years, the child was significantly delayed in development. The obstetrician, birthing hospital, and referral hospital were sued. The case settled without going to trial.

CASE 2

A 40-week gestational age female infant with a birthweight of 3,325 g was born to a 39-year-old gravida 2 para 1 woman with a pregnancy complicated by pregnancy-induced hypertension and group B *Streptococcus* colonization. The woman received ampicillin 3 hours before delivery. The fetus was in the occiput posterior position. Artificial rupture of membranes occurred 7 hours before delivery and the fluid was clear. The vacuum was applied at +1 station, but no descent occurred. After 10 pulls with the vacuum, the variability on the fetal heart tracings became minimal and the fetal heart rate rose to 180 beats/min. After the 10th vacuum pull, the attempt to deliver vaginally was abandoned and the fetus was delivered by cesarean. ***The plaintiff obstetrician was critical about the station at which the vacuum was applied. The obstetrician noted that the vacuum should not have been repeated because no descent was achieved and stated that to repeat it after the first application without descent was below standard of care. The obstetrician added that to repeat it 10 times was egregious.*** The Apgar scores were 7 and 8, at 1 and 5 minutes, respectively. The infant was noted to be floppy and pale and had a very swollen head. She was sent to the newborn nursery. ***The plaintiff neonatologist was critical of sending an infant to the newborn nursery while she was pale and floppy with a swollen head. This infant, he contended, needed an evaluation and intensive care to monitor her vital signs including blood pressure and hematocrit. He pointed out that the history of vacuum pulls and the infant's clinical findings of paleness and scalp examination fit perfectly with a diagnosis of subgaleal hemorrhage.***

Because the scalp swelling, paleness, and hypotonia continued in the newborn nursery, the nurse contacted the neonatologist. The infant was admitted to the NICU at 1 hour of age. Her capillary refill was prolonged, pulses could not be palpated, heart rate was 152 to 160 beats/min, and diastolic blood pressures ranged from 16 to 19 mm Hg with mean blood pressures in the high 20s. ***The plaintiff neonatologist said that an immediate red blood cell transfusion should have been given with emergency release blood.*** A capillary blood gas showed a pH of 7.27, P_{CO_2} of 27 mm Hg (3.6 kPa), P_{O_2} of 56 mm Hg (7.4 kPa), and base excess of −12.9. The complete blood cell count was unremarkable except for a hematocrit of 27%. The neonatologist (out of the hospital) was informed of the various laboratory and blood pressure values. No orders were given. Two hours later, a nurse recontacted the neonatologist to inform him that the infant's head circumference had increased from 36 cm at birth to 38 cm. Three hours after birth, the neonatologist ordered a CT scan that showed bilateral diffuse scalp edema and a subgaleal hematoma, but no intracranial abnormalities. The nurse again informed the neonatologist about the low blood pressures and the CT findings. At this point, the neonatologist ordered a cross and type match for packed red blood cells and 30 mL of normal saline. ***The plaintiff neonatologist was critical of the neonatologist for not coming to the bedside when he was informed of the infant's condition on admission to the NICU. The standard of care required the neonatologist to immediately examine the infant and place umbilical lines, order a blood gas and complete blood cell count, and intervene with a blood transfusion.*** At 4 hours of age, a transfusion was started. The infant's second blood gas was drawn at 5 hours and showed a pH less than 6.8, P_{CO_2} of 15 mm Hg, P_{O_2} of 53 mm Hg, and an incalculable base deficit. Two hours later, a second transfusion was started and umbilical lines were placed by the neonatologist at 6½ hours of age. Over the next 4 hours, multiple blood transfusions were provided. The urine output had diminished and the infant's laboratory findings were as follows: creatinine, 1.5 mg/dL (132.6 μmol/L); aspartate aminotransferase, 3,288 U/L (55 μkat/L); alanine aminotransferase, 1,535 U/L (26 μkat/L); and lactate, 10.3 mg/L (1.1 mmol/L). The infant developed disseminated intravascular coagulopathy. Her head circumference increased 2.5 cm over the next few hours. At this point, 12 hours after birth, a referral hospital was asked to admit this infant.

At the referral hospital, the infant's acute renal failure and liver failure were managed with intraperitoneal dialysis. Her creatinine peaked at 4.7 mg/dL (415 μmol/L), and her urine output eventually resumed. Her bilirubin peaked at 14.5 mg/dL (248 μmol/L) with a conjugated bilirubin of 12.8 mg/dL (219 μmol/L), which eventually normalized. She was started on hydrocortisone treatment for 6 weeks for adrenal failure. She was given high-frequency oscillatory ventilation because of fluid overload secondary to the renal failure.

Initially, she required inotropic support for hypotension, but later developed systemic hypertension that was managed with hydralazine. A gastric tube was placed because of poor feeding. At age 4 years, the child had serious neurodevelopmental issues, hypertension, and continued need for gastric tube feedings. The obstetrician, neonatologist, and hospital were sued. The case settled without going to trial.

CASE 3

A 40 3/7–week gestational age male infant with a birthweight of 3,025 g was born to a 26-year-old gravida 1, para 0 woman with an unremarkable pregnancy. Membranes ruptured 16 hours before birth with clear fluid. Labor ensued, but did not progress secondary to cephalopelvic disproportion and occiput transverse malposition. The obstetrician decided to use a vacuum, which he applied 3 times, without any fetal descent. ***The plaintiff obstetrician was critical of the application of the vacuum the second time because no descent had been appreciated. The treating obstetrician said the infant did descend, he just did not remember to document it. The plaintiff obstetrician pointed out that the application 3 times was below standard of care and that any movement of the head that the treating obstetrician claimed occurred was probably as a result of the skull fracture that he created, as evidenced by the CT scan taken later. The nursing documentation showed that the fetus was at exactly the same position before and after the vacuum pulls. The mother and father stated at their depositions that the obstetrician had his feet on the delivery table to help increase the force of his pulls. The plaintiff obstetrician stated that this was unconscionable to apply that amount of force to a fetal head.*** The infant was born by cesarean. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The infant was noted to be pale at birth. At 15 minutes of age, the nurse noted molding, and overriding sutures with a caput succedaneum. The infant was transferred to the newborn nursery. ***The father, at his deposition, said that he noted shaking movements of the infant's left arm and leg at a few hours of age, but when he communicated this to the nurse, she said it was normal. He added that between 30 and 36 hours after birth, he saw his infant shaking and thought it was not normal. Again, the nurse reassured him.*** An hour later (~37 hours of age), the father brought the nurse to observe what he was concerned about, and the nurse immediately brought the infant to the NICU where seizure activity was confirmed. ***The plaintiff neonatologist pointed out that seizures can be deleterious to the brain through several mechanisms that result in brain cell loss and altered brain cell development. He pointed out that if the nurse had called the physician to discuss the situation, as the standard of care required, the infant could have been properly evaluated and monitored. The plaintiff neonatologist stated that the infant was at high risk for neurologic abnormalities with a failed vacuum attempt and the father's observations should have been taken more seriously. The defense countered that jitteriness was very common in newborns and it was reasonable that the nurse used her judgment by not calling a physician. He said that the lack of a bulging fontanel was reassuring.***

The evaluation of the infant's seizures consisted of a lumbar puncture, which showed a white blood cell count of 1,358/μL (1.36×10^9/L), red blood cell count of 10.5×10^6/μL (10.5×10^9/L), polymorphonuclear leukocyte count of 65%, protein of 0.119 g/dL (1.19 g/L), and glucose of 65 mg/dL (3.6 mmol/L). A head CT showed a large subdural hematoma with a mass effect on the right parietal, temporal, and occipital lobes, and multiple calvarial fractures as well as a right frontoparietal scalp hematoma. ***The obstetrician retained by the defense said that the head trauma was a result of a normal birthing process when the fetal head comes in contact with the maternal bony pelvic bones. Plaintiff experts strongly disagreed that these fractures could be found in a normal birthing process, but rather, were clearly the result of the excessive force from the vacuum. They noted that sometimes a linear skull fracture can be found as a result of a normal birthing process, but no one would expect multiple skull fractures or a massive subdural hematoma following a normal birth.*** The neurosurgeon immediately brought the infant to the operating room for an emergency evacuation of the subdural hematoma. The cerebral edema was so massive that a right hemicraniectomy with a frontal parietal patch was necessary to achieve closure of the skull. Hypothermia for neuroprotection was initiated after the surgery. The infant had a difficult course after surgery with seizures that were difficult to control. He was discharged from the hospital at 1 month of age with levetiracetam and phenobarbital treatment, and wearing a protective molding helmet. He needed a gastric tube because he could not feed orally. He required 2 cranioplasties with cranial vault reconstruction. On follow-up at 6 years, he had persistent left-sided weakness, mild spastic hemiparesis, and delays in gross and fine motor, language, and social development skills. The obstetrician was sued. The case was arbitrated and the defense won.

DISCUSSION

Case 1

An iatrogenic encephalocele should be suspected in infants treated with instrumentation, who have a scalp that remains swollen despite the passage of a few days. CT or MRI should be considered for infants who have sustained head trauma in which the diffuse swelling does not subside. Cranial ultrasonography is not the neuroimaging of choice for an evaluation of a swollen scalp. Caput succedaneum is a frequently occurring swelling from serum or blood that accumulates above the periosteum. The extravasation results from the higher pressure of the uterus or vaginal wall on those areas of the presenting part of the fetal head that border the caput. It markedly improves within 24 hours and almost always resolves 48 to 72 hours after birth without sequelae. Imaging should be considered in every child with a swelling of the scalp that does not diminish in 48 to 72 hours or with any enlargement more than 24 hours after delivery. Rarely, a hemorrhagic caput may result in severe hypotension. Cephalohematomas may not be apparent for several hours or days after birth because the bleeding is subperiosteal, and therefore is a slowly developing process. Because the bleeding is contained between the bone and the periosteum, a sharp demarcation without crossing suture lines is notable and makes this lesion distinguishable from other scalp lesions after birth. The incidence is 0.4% to 2.5% of live births, with a higher frequency in infants born to primiparous mothers. Cephalohematomas may be associated with more severe forms of intracranial trauma, especially if bilateral. Indirect hyperbilirubinemia is a common complication of a cephalohematoma. Because the elevated bilirubin may not be apparent at the time of discharge, close monitoring of bilirubin levels in these infants is very important. Affected infants rarely have significant bleeding, but a rare case of profound anemia has been reported.

Case 2

Subgaleal hemorrhage should be suspected in difficult deliveries, especially instrument-assisted births. The overall incidence of subgaleal hemorrhage is 1 in 2,000 births, but it is 10 times higher in vacuum-assisted deliveries. Infants with subgaleal hemorrhages have the largest risk for acute blood loss because the subgaleal space is composed of loose connective tissue, allowing the bleeding to expand and extend, even accommodating nearly the entire neonatal blood volume in a term infant. Significant hypovolemia and anemia may present with a rapid onset. If significant subgaleal hemorrhage develops in the fetus ***long before*** the actual birth, the infant may be extremely pale and in shock at the time of birth. If significant subgaleal hemorrhage occurred ***just before*** delivery, then the infant may not appear as pale or be in shock, but will develop this over a short time frame. These infants often are not in the NICU because they appear relatively intact immediately after birth. If the amount of blood loss is minor, then volume replacement with normal saline may be appropriate. If significant bleeding has occurred, as indicated by hypotension, poor perfusion, and paleness, emergency blood is critical. If blood is not administered in a timely manner in this scenario, encephalopathy (hypotonia, lethargy, apnea, seizures) and multiorgan damage will ensue. The kidneys are very vulnerable to hypovolemic anemia; if intervention is not timely, severely affected infants often require dialysis and eventually kidney transplantation.

Case 3

Subdural hemorrhage occurs in nulliparous women with an unassisted vaginal delivery with an incidence of 2.9 per 10,000 deliveries. The incidence is significantly increased to 8 and 9.8 per 10,000 deliveries for vacuum-assisted and forceps-assisted deliveries, respectively. The sequential use of vacuum and forceps increases the risk to 21.3 per 10,000 deliveries. Subdural hemorrhages are highly associated with breech deliveries. The location and extent of the subdural hemorrhage determines if it is just a coincidental finding or if it is causing neurologic injury. Symptoms usually begin within the first 24 to 48 hours of age and include seizures, apnea, irritability, and altered tone and level of consciousness. The plasticity of the neonatal skull allows for some degree of expansion without the development of increased intracranial pressure. In cases with a mass effect or when the subdural hemorrhage occurs in the posterior fossa where skull plasticity is less, emergent surgical evacuation is necessary to avoid brainstem compression.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the indications for and perinatal complications of operative vaginal delivery (forceps, vacuum extraction, etc) and of vaginal delivery after cesarean delivery.
- Understand the pathogenesis, clinical and imaging features, diagnosis, management, and outcome associated with subdural hematoma.
- Know the diagnostic, clinical, and imaging features of extracranial hemorrhage, including cephalohematoma and subgaleal hemorrhage.

Suggested Readings

Jeltema HR, Hoving EW. Iatrogenic encephalocele: a rare complication of vacuum extraction delivery. *Childs Nerv Syst*. 2011;27(12):2193–2195

Rosenberg A. A traumatic birth injury. *NeoReviews*. 2003;4:e270–e276

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Preterm Premature Rupture of Membranes in the Periviable Gestation and Placental Abruption

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal values for arterial umbilical cord gas values and indications of acidosis are defined in the Table.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min

AUTHOR DISCLOSURE Drs Cheng and Spiel have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. **Arterial Umbilical Cord Gas Values**

	pH	Pco_2 (mm Hg)	Po_2 (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤–10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤–10
Metabolic acidosis	<7.20	<60	Variable	≥–10
Mixed acidosis	<7.20	>60	Variable	≥–10

*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695.

- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:
  - Absent: Amplitude range is undetectable
  - Minimal: Amplitude range is greater than undetectable to 5 beats/min
  - Moderate: Amplitude range is 6–25 beats/min
  - Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline
- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - □ Recurrent late decelerations
    - □ Recurrent variable decelerations
    - □ Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

A 27-year-old gravida 3, para 1-0-1-1 woman at 23 weeks 4 days' gestation, with good dating, presented to her primary obstetric provider with a history of fluid leakage for 2 weeks. During this period, she had received multiple speculum examinations, results of which were negative for rupture of membranes. Her prenatal course was complicated by bacterial vaginosis infection and trichomonas, both of which were treated. She had a remote history of recurrent chlamydia infection. Her obstetric history was notable for a prior full-term vaginal delivery, which was complicated by postpartum preeclampsia with severe features. Her social history was notable for multisubstance use, but she had no history of cocaine use.

In the physician's office, the fetus was frank breech with an amniotic fluid index of 4. Her group B *Streptococcus* (GBS) status was unknown. Because of the gestational age, she was transferred to a tertiary care center with a level III NICU.

CASE PROGRESSION

Upon arrival, the patient's admission examination revealed a young woman in no acute distress. Her abdomen was soft, mildly tender to palpation near the umbilicus, without rebound tenderness or guarding. She had no uterine tenderness. Uterine tocometry did not demonstrate contractions. A sterile speculum examination demonstrated a closed cervix with pooling of clear fluid, which was nitrazine and fern positive. Given the confirmed preterm premature rupture of membranes (PPROM), latency antibiotics were initiated. Her evaluation for PPROM was unremarkable except for a urine screen that was positive for marijuana. She remained afebrile. Ultrasonography revealed a singleton gestation with an estimated fetal weight of 565 g in variable lie, with subjectively low amniotic fluid, as well as an anterior previa with the edge of the placenta abutting the internal os. The cervix was also closed, measuring 3 cm and with no evidence of funneling.

Given the periviable gestational age, neonatology and maternal-fetal medicine were jointly consulted to discuss options for obstetrical and neonatal management. After this discussion, the patient elected for full obstetric and neonatal intervention. During her antepartum course, her GBS culture result was negative, and her placenta previa resolved. At 27 weeks' gestation, she had increased vaginal bleeding and soaked through 3½ pads. A speculum examination showed minimal blood in the vault and a visually closed cervix. Bedside ultrasonography also confirmed cephalic presentation and no sonographic evidence of abruption. The fetal heart tracing at the time of the bleeding is displayed in Fig 1.

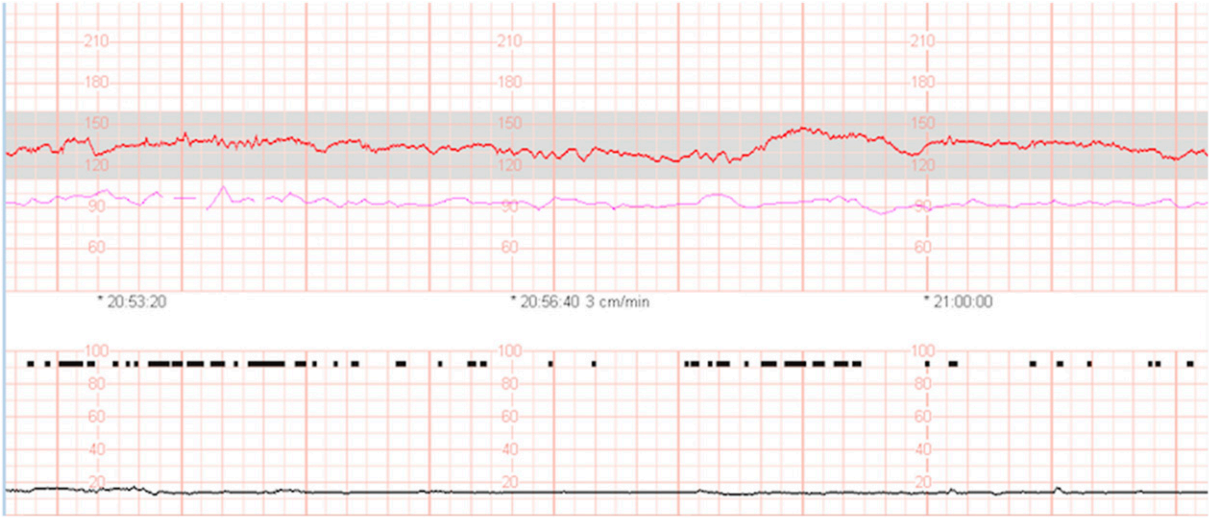

Figure 1. External fetal monitoring strip 1.

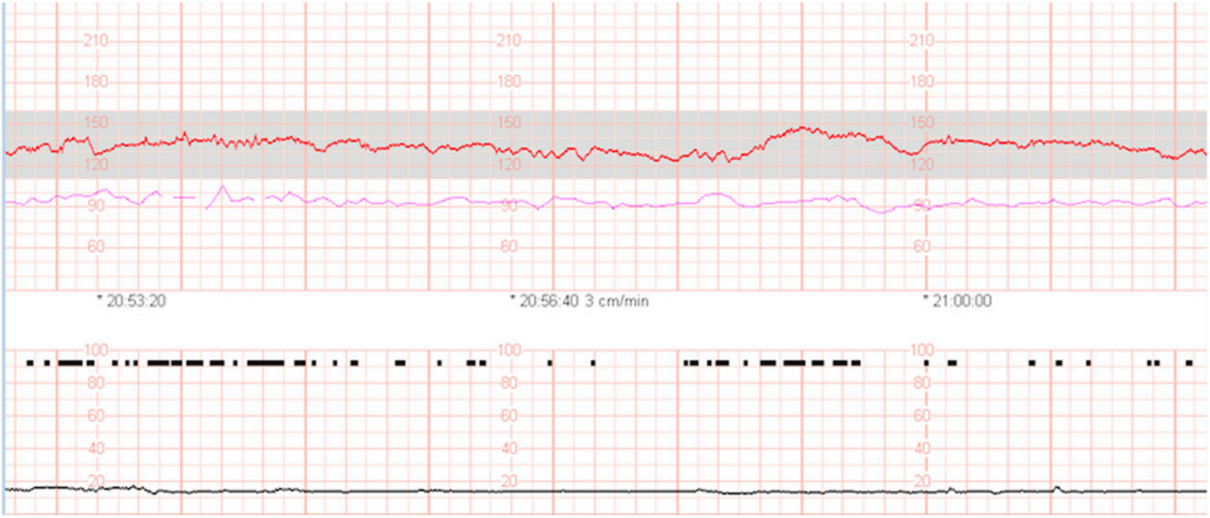

Figure 1. External fetal monitoring strip 1.

Interpretation of Fig 1:

- Variability: Moderate
- Baseline rate: 135 beats/min
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category I
- Differential diagnosis: Normal fetal status and placental abruption
- Action: The patient was transferred to the labor and delivery department for continuous monitoring

After 24 hours of stability, continuous monitoring was discontinued. At 27 and 3/7 weeks' gestation, she had increased bleeding and returned to labor and delivery. Her hematocrit decreased from 34% to 30%. A representative fetal monitoring strip is demonstrated in Fig 2.

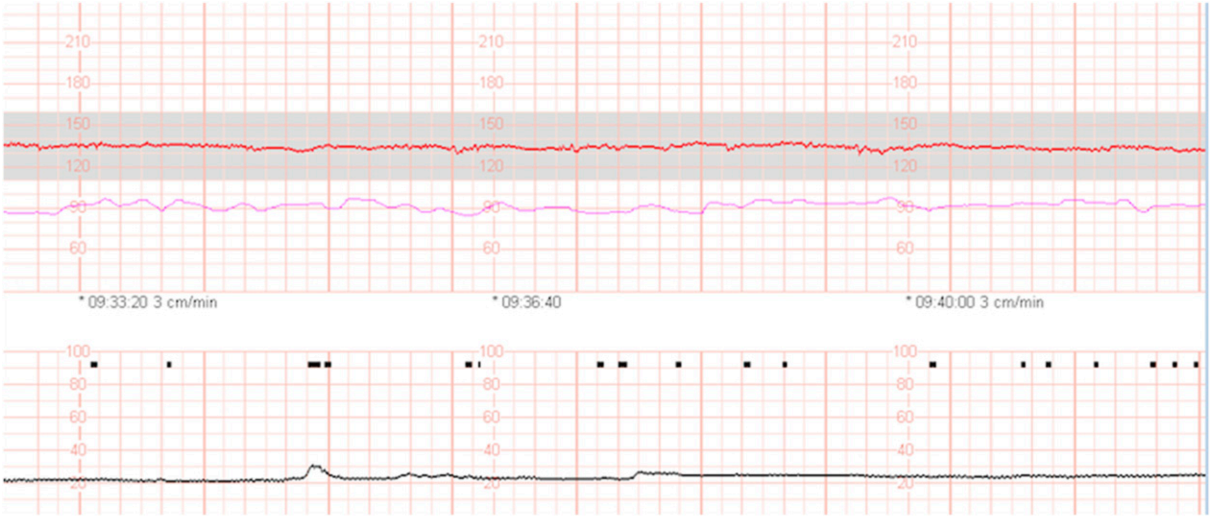

Figure 2. External fetal monitoring strip 2.

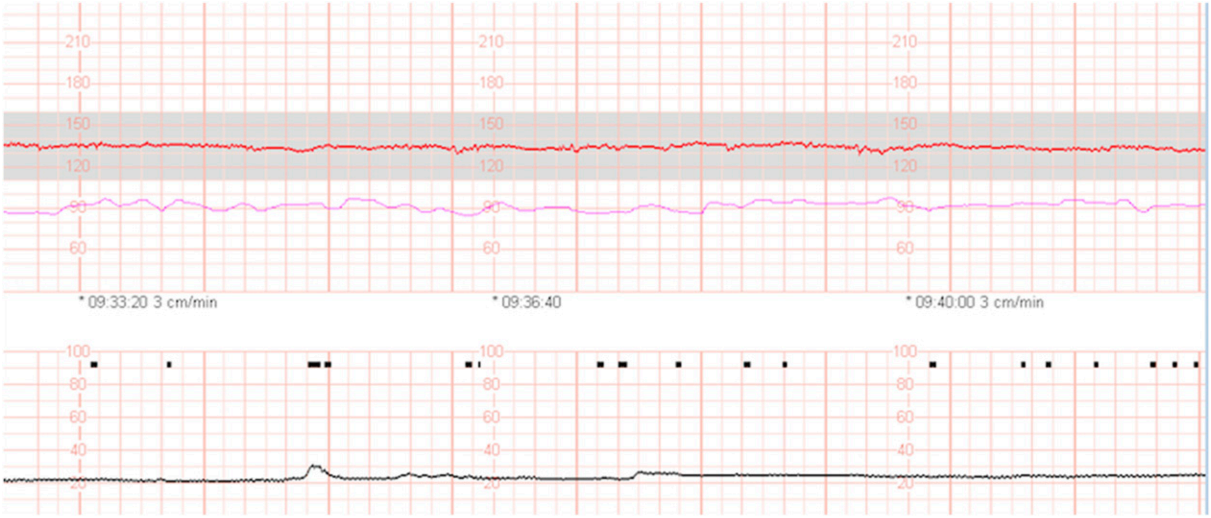

Figure 2. External fetal monitoring strip 2.

Interpretation of Fig 2:

- Variability: Minimal
- Baseline rate: 135 beats/min
- Episodic pattern: None
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Uteroplacental insufficiency from a suspected abruption or fetal sleep cycle
- Action: Continuous monitoring and follow-up ultrasonography (still without ultrasonographic evidence of abruption)

Given the concern for worsening placental abruption and change in fetal status in the setting of PPROM, delivery was recommended. The fetus was cephalic and an oxytocin contraction stress test was performed. After 10 minutes, the fetal heart tracing is demonstrated in Fig 3.

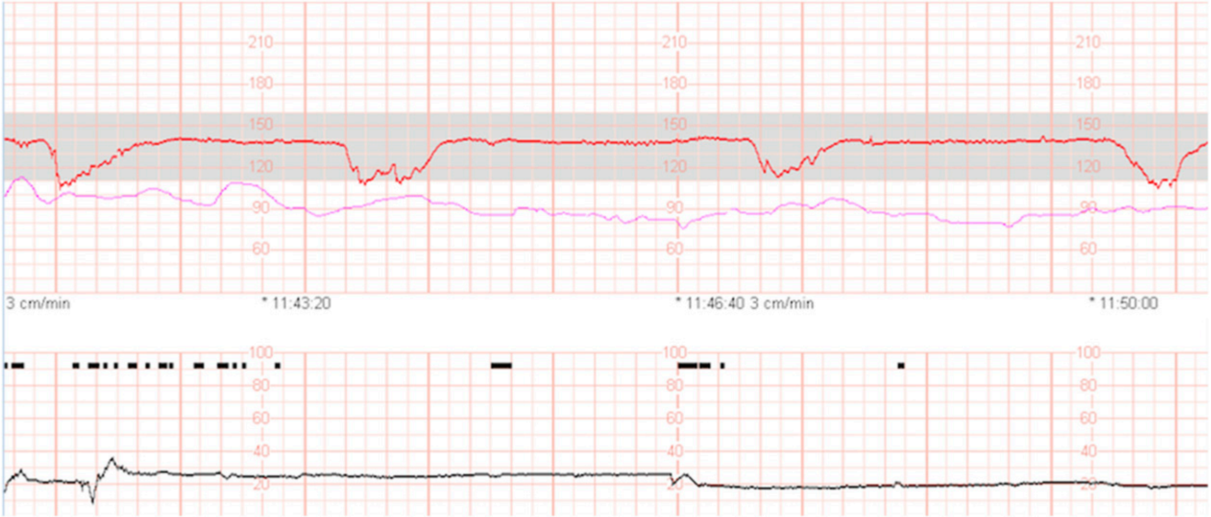

Figure 3. External fetal monitoring strip 3.

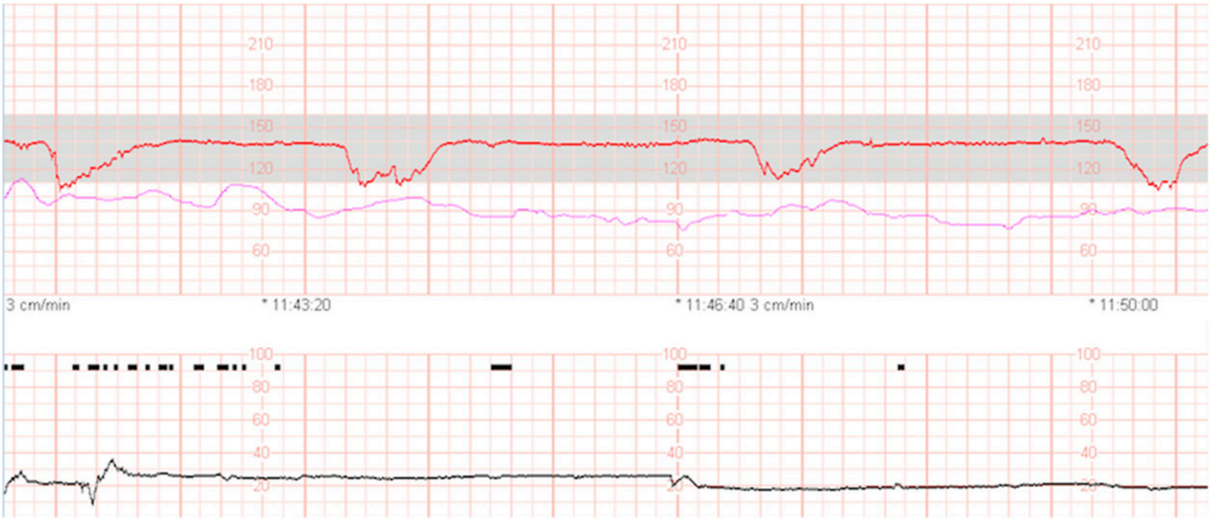

Figure 3. External fetal monitoring strip 3.

Interpretation of Fig 3:

- Variability: Minimal
- Accelerations: None
- Baseline rate: 140 beats/min
- Episodic patterns: Variable decelerations
- Periodic patterns: None
- Uterine contractions: None visible but palpated externally for intensity and frequency
- Interpretation: Category II
- Differential diagnosis: Abruption, fetal hypoxemia or acidosis, umbilical cord compression
- Action: Oxytocin infusion was discontinued and cesarean delivery was performed

OUTCOME

Upon administration of adequate spinal anesthesia in the operating room, the FHR dropped to the 80s on quick assessment. The patient underwent an emergent primary low transverse cesarean section for delivery of a 27 3/7–week gestational age male neonate with a triple nuchal cord. Apgar scores were 6 and 7 at 1 and 5 minutes, respectively. Cord gas was deferred, given the 5-minute Apgar score of 7. The neonate weighed 1,040 g (57th percentile). A large retroplacental clot was noted. During the resuscitation, the neonate received continuous positive airway pressure followed by positive pressure ventilation because of the inconsistent respiratory effort and periods of apnea. He subsequently required intubation and received 3 doses of surfactant.

The infant's neonatal intensive care course was complicated by *Staphylococcus aureus* bacteremia requiring reintubation on day 35 after birth, as well as a septic ileus that was treated with vancomycin, piperacillin, and tazobactam, which was later changed to nafcillin. Cerebrospinal fluid, abdominal ultrasonography, ophthalmologic examinations, and cardiac echocardiography findings were all normal; urine testing for cytomegalovirus also had negative results. He also developed an unconjugated hyperbilirubinemia requiring phototherapy. Head ultrasonographic scans were all within normal limits.

Placental pathology showed a small hypermature placenta at less than the 10th percentile for 27 weeks' gestation, hypertrophic decidual vasculopathy, distal villous hypoplasia, umbilical cord funisitis, and meconium-laden macrophages.

DISCUSSION

This case raises questions about periviable management and PPROM with placental abruption.

A 2017 obstetric care consensus (developed jointly by the ACOG and the Society for Maternal-Fetal Medicine) about an anticipated or inevitable periviable birth states that "obstetric interventions should be undertaken only after a discussion with the family regarding individual risks and benefits of management options in addition to alternate approaches." (1) For our patient who presented at 23 weeks and 4 days, this conversation was imperative. However, not only is the act of discussion important, but the consensus stressed that "this discussion should include an unbiased presentation of data related to the chance of both survival and long-term neurodevelopmental impairment… [and] also should present the option of nonintervention."(1) At our institution, this discussion is performed jointly with neonatologists and maternal-fetal medicine specialists to ensure unbiased uniform counseling. In situations in which death or significant neurodevelopmental impairment is probable, it has also been emphasized that "parents should be given the choice for palliative care and [termination…as informed by local institutional policy and relevant laws] alongside the option to attempt resuscitation." (1) After our initial discussions with the patient, she expressed a desire for maternal and neonatal intervention. However, it is important to discuss with the patient the choice of interventions, which should be guided by the clinical picture and increasing gestational age. Of note, initiating one form of intervention does not mandate all other forms of intervention, which could include tocolysis to allow for administration of antenatal steroids, administration of latency antibiotics for PPROM or GBS prophylaxis, or proceeding with a delivery. (1) The decision to initiate the use of continuous electronic FHR monitoring should be made in concert with the plan for intrauterine resuscitation and delivery. Because of limited data on implementing these interventions at less than 24 weeks' gestation, recommendations for management have been extrapolated from data collected from patients who delivered between 26 and 34 weeks of gestation. (1) For gestational age between 23 0/7 weeks and 23 6/7 weeks, the consensus has made less directive recommendations, with the use of language such as "consider" for the aforementioned obstetric interventions.

For our patient, who initially presented at 23 4/7 weeks' gestation with PPROM in the absence of labor, latency antibiotics and betamethasone were administered, but magnesium sulfate and tocolysis were deferred. Magnesium sulfate was deferred because the patient was remote from delivery. Tocolysis was also deferred because of the potential risk for prolonging a pregnancy with subclinical chorioamnionitis. (2) During the periviable period, our patient remained stable without evidence of chorioamnionitis. At 27 and 0/7 weeks' gestation, she had vaginal bleeding concerning for placental abruption and was started on magnesium treatment for fetal neuroprotection and received a repeat course of antenatal corticosteroids after extensive counseling. (3) According to the 2015 Cochrane meta-analysis on neonatal outcomes after a repeat course of corticosteroids (7 days from initial course) in women who are at risk for preterm delivery before 34 0/7 weeks' gestation, results demonstrated a reduction in respiratory distress syndrome with only a small reduction in size at birth and no significant adverse outcomes. (4) Of note, a repeat betamethasone course is not routinely administered in the setting of PPROM because of concerns about chorioamnionitis and the limited benefit. Currently the evidence is insufficient for recommending a rescue course of corticosteroids in the setting of PPROM. In a study conducted by Gyamfi-Bannerman and Son, there was no difference in the incidence of neonatal sepsis among neonates exposed to PPROM and who were born to women who received either 1 or 2 courses of steroids. (5) However, further investigation is warranted to determine the potential benefits of 2 courses instead of 1 course of betamethasone in this population. This patient discussed these risks and benefits with the providers and decided to receive a rescue course.

Placental abruption is defined as the premature separation of a normally implanted placenta. This condition complicates approximately 1% of all deliveries; however, there is significant discrepancy between pathologic and clinical diagnosis of abruption. (6) Placental pathologic examination has estimated the incidence of abruption at 3.8%, though it does not typically correlate with any clinically significant consequences. (7)(8) Up to 10% of preterm births involve an abruption. (9) In acute severe cases, placental abruption can be an indication for preterm delivery, before the onset of labor, given the risks of oxygen and nutrition deprivation to the fetus. (6) PPROM is a known risk factor for abruption and the mechanism may be attributable to sudden uterine decompression from membrane rupture, resulting in disruption of the decidual spongiosa layer, where the placenta is attached. (6)(10) A dose relationship between the time of membrane rupture and the risk of abruption in women diagnosed with PPROM has also been described. (11) Other risk factors for placental abruption include chronic hypertension, preeclampsia, cocaine and drug use, oligohydramnios, chorioamnionitis, multiple gestation, cigarette smoking, and maternal age and parity. (6) This patient had prolonged PPROM and oligohydramnios, but did not share the remaining risk factors.

Typically, placental abruption is a clinical diagnosis including vaginal bleeding and/or abdominal pain and/or low-amplitude high-frequency contractions. The degree and severity are difficult to evaluate clinically, because the amount of vaginal bleeding and FHR patterns are variable. (6)(12) The use of ultrasonography to confirm placental abruption is not sensitive, because only 1 in 9 ultrasound scans of suspected abruption demonstrate subchorionic or retroplacental hematoma. (13) Among cases of confirmed placental abruption at the time of delivery, only 25% had positive ultrasonographic findings previously. (13) However, when the scan-to-delivery interval was 14 days or fewer, the positive predictive value of ultrasonography is increased. (13) One plausible explanation for this is that if a large enough volume of blood is visualized on ultrasonography, it is less likely to be completely drained or resorbed by the time of delivery. (13) FHR patterns may demonstrate reduced variability, variable or late decelerations, and in severe fetal distress, bradycardia or sinusoidal pattern. (6) Interestingly, 3 of these heart rate patterns were noted in the current case on the day of delivery: decreased variability, variable decelerations, and bradycardia. In this case, FHR tracing, vaginal bleeding, and ultrasonography were all used to facilitate decision making for delivery. For this patient, the positive result on the oxytocin contraction stress test demonstrated that the fetus was unlikely to tolerate induction of labor to allow for a vaginal delivery. Thus, a cesarean delivery was performed without complication. The clinical findings of a large retroplacental clot at delivery as well as the pathologic analysis confirmed the diagnosis of abruption.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes, complications, and management of preterm premature rupture of membranes.

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Black Eschar on a 4-day-old Preterm Infant

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Mouied Alashari, MD,‡ Belinda Chan, MD*

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THE CASE

A 4-day-old female neonate presented with a black necrotic lesion with circumferential ulceration and erythema located to the left of the umbilicus.

Prenatal and Birth Histories

- Female infant born to a 31-year-old gravida 1, para 0 woman
- Maternal medications included prenatal vitamins; uncomplicated pregnancy without infections, exposures, genital lesions, smoking, alcohol, or drug use
- No risk factors noted for congenital infections with normal maternal prenatal screenings
- Normal fetal survey conducted via ultrasonography at 20 weeks' gestation
- Pregnancy complicated by intrauterine growth restriction and fetal distress with absent end diastolic blood flow noted before delivery
- Also complicated by severe preeclampsia and mild thrombocytopenia with platelet count $134\times10^3/\mu L$ ($134\times10^9/L$) at 27 4/7 weeks' gestation; treated with betamethasone, magnesium, labetalol, and nifedipine
- Infant delivered at 27 5/7 weeks' gestation via cesarean delivery due to fetal distress
- Artificial rupture of membranes 1 minute before delivery with clear fluid; Apgar scores 3 and 9 at 1 and 5 minutes, respectively
- Infant required positive pressure ventilation and intubation during resuscitation

Presentation

The infant was admitted to the NICU. An umbilical venous catheter (UVC) was inserted with the use of betadine as the antimicrobial skin preparation and a thin hydrocolloid dressing (DuoDERM®, ConvaTec, Bridgewater, NJ) as a protective skin barrier to secure the UVC. The hydrocolloid dressing was located just left of the umbilicus and placed on intact abdominal skin.

The infant was noted to have asymptomatic thrombocytopenia (platelet count $73{,}000/\mu L$ [$73\times10^9/L$]) and neutropenia (absolute neutrophil count $700/\mu L$ [$0.70\times10^9/L$]), which were attributed to maternal preeclampsia. The infant received 1 dose of granulocyte colony-stimulating factor (G-CSF, 10 $\mu g/kg$, subcutaneously) at 2 days of age. Prophylactic antibiotics were not indicated at the time of birth because there were no concerns for infection.

The infant underwent extubation to receive nasal noninvasive ventilation within 24 hours of birth. At 4 days of age, she developed persistent apnea and episodes of bradycardia necessitating reintubation. Chest radiography was

AUTHOR DISCLOSURE Drs Murphy, Yost, Short, Alashari, and Chan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

performed before intubation, which showed that the UVC had migrated with the tip below the diaphragm (Fig 1). The malpositioned UVC and its dressing were removed, revealing a black skin lesion measuring 1×1.5 cm on the left anterior abdominal wall.

Blood and wound culture specimens were obtained. Antibiotic and antifungal treatments were initiated immediately with vancomycin, cefepime, and fluconazole. The lesion continued to progress in size, measuring 3.25×2.75 cm at 6 days of age. The lesion had the appearance of a black eschar with circumferential ulceration, erythema, and scattered white patches along the erythematous edges (Figs 2 and 3).

The infant remained intubated and required high-frequency oscillatory ventilation. During this time, the infant had no other systemic signs of illness. She had stable vital signs and normal inflammatory markers, white blood cell counts, and platelet counts.

Vital Signs (6 days of age)

- Temperature: 98.06°F (36.7°C)
- Heart rate: 164 beats/min
- Blood pressure: 76/55 mm Hg
- Weight: 770 g (10th percentile); length: 32.5 cm (3rd percentile)

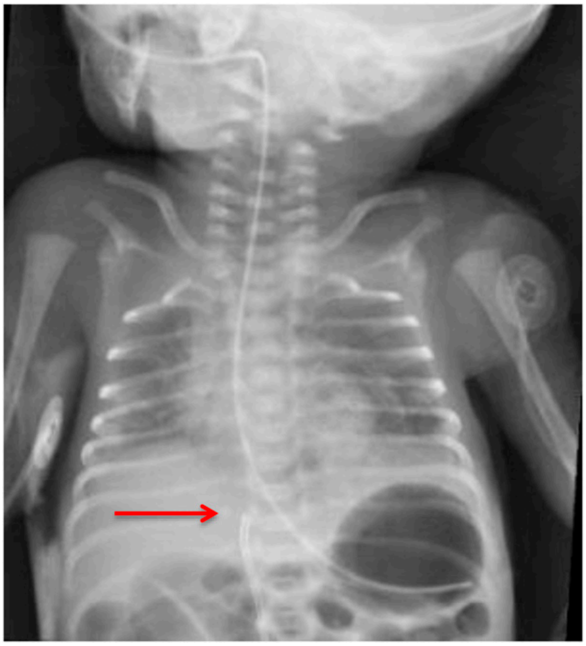

Figure 1. The infant's chest radiograph with the arrow pointed at the tip of the umbilical venous catheter, which was below the diaphragm.

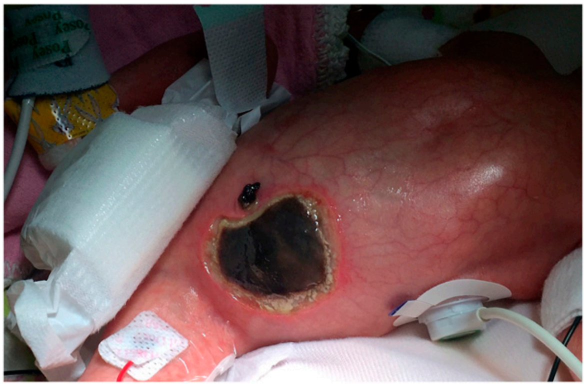

Figure 2. Black eschar seen in the 6-day-old infant.

Physical Examination (6 days of age)

- Head: Normocephalic, anterior fontanelle open, soft, and flat, no scleral injection, no oral lesions, oral endotracheal tube secured in place
- Lungs: Clear breath sounds bilaterally with mild intermittent subcostal retractions
- Cardiovascular: Regular heart rate without murmur, capillary refill <3 seconds
- Abdomen: Soft, round, normoactive bowel sounds, no hepatosplenomegaly, 3.25 × 2.75-cm black eschar is noted to the left of the umbilicus with lateral extension away from the umbilicus onto the skin of the left lower quadrant; circumferential ulceration with white patches surround the black eschar
- Genitourinary: Normal preterm female genitalia and patent anus
- Extremities: No deformities
- Neurological: Normal tone and activity for gestational age
- Skin: Immature translucent skin with visible veins, skin lesion as described

Laboratory Studies

- White blood cell count: $21\times10^3/\mu L$ ($21\times10^9/L$) with 19% neutrophils, 22% bands, 11% lymphocytes, 27% monocytes, and 6% eosinophils (note: these results were obtained 4 days after G-CSF administration)
- Hemoglobin: 11.9 g/dL (119 g/L)
- Platelet count: $161\times10^3/\mu L$ ($161\times10^9/L$)
- C-reactive protein: 1.0 mg/L (9.52 nmol/L)
- Electrolytes and transaminases: Within normal ranges

Differential Diagnosis

- Necrotizing fasciitis
- Purpura fulminans
- Cutaneous fungal infection
- Cutaneous herpetic infection

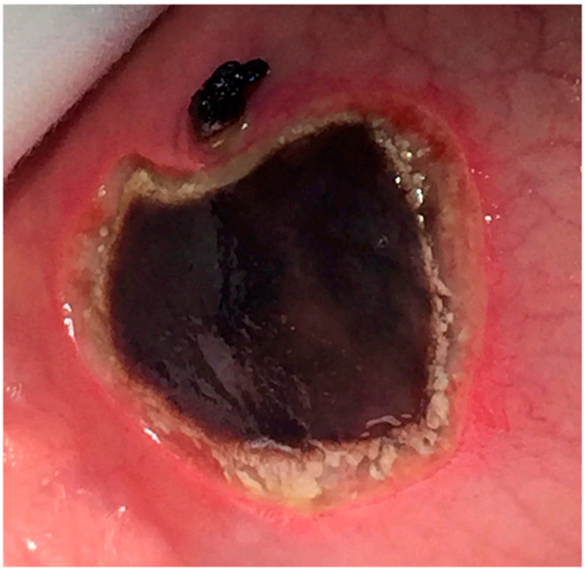

Figure 3. Close-up view of the skin lesion.

- Omphalitis
- Chemical burn
- Pressure ulcer
- Intravenous (IV) extravasation of prior infusion
- Langerhans cell histiocytosis

Actual Diagnosis

Cutaneous *Rhizopus* infection

EVALUATION AND MANAGEMENT

Because of the persistent expansion and necrotizing nature of the lesion, the consulting pediatric plastic surgeon suspected full thickness involvement of the anterior abdominal wall. The infant was transferred to a level IV NICU for surgical debridement. The operative note indicated that the necrotizing lesion involved the skin, subcutaneous tissues, anterior fascia, a portion of the rectus muscle, and the external oblique fascia (Fig 4). Skin biopsy specimens were obtained for culture and histopathologic evaluation. The initial and intraoperative wound cultures were positive for 1+ coagulase-negative *Staphylococcus* and *Rhizopus* species. Histopathologic evaluation confirmed the presence of *Rhizopus* species in the subcutaneous tissue with Grocott methenamine silver stain (Fig 5).

The infant was initially treated with voriconazole while awaiting the results of the (1-3)-β-D-glucan (Fungitell®; Associates of Cape Cod Inc, East Falmouth, MA) and galactomannan testing. The positive Fungitell test result with a (1,3)-β-D-glucan level of more than 500 pg/mL (negative is <31 pg/mL) strongly suggested fungal infection. *Aspergillus* galactomannan antigen testing was negative. The coagulase-negative *Staphylococcus* isolates from the wound culture were considered a contaminant. Blood and urine cultures remained negative for both bacteria and fungi. As recommended by the infectious disease service, abdominal, cranial, and cardiac ultrasonography as well as an ophthalmologic examination was performed; there was no sign of disseminated fungal disease because all of these test results were negative. Treatment was changed to liposomal amphotericin and the infant completed a 14-day course of antifungal therapy. The infant's thrombocytopenia and neutropenia (thought to be secondary to maternal preeclampsia) improved before the initiation of antifungal therapy, with normalization by 14 days of age. Following surgical debridement and appropriate antifungal therapy, the infant's wound continued to heal well (Fig 6). *Rhizopus* species are an uncommon source of fungal infections in neonates. The presence of *Rhizopus* infection within the NICU prompted a hospital-wide infectious and epidemiologic investigation to identify possible sources. A thorough investigation failed to identify the source of this infant's *Rhizopus* infection.

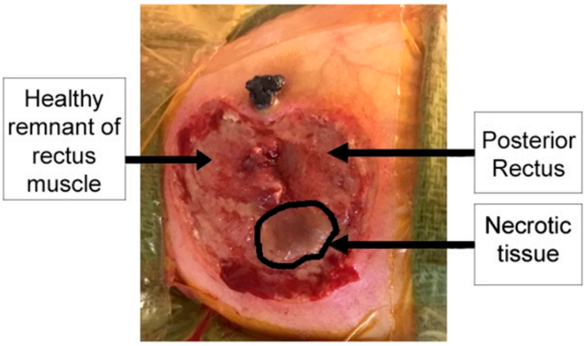

Figure 4. Intraoperative photograph during surgical debridement.

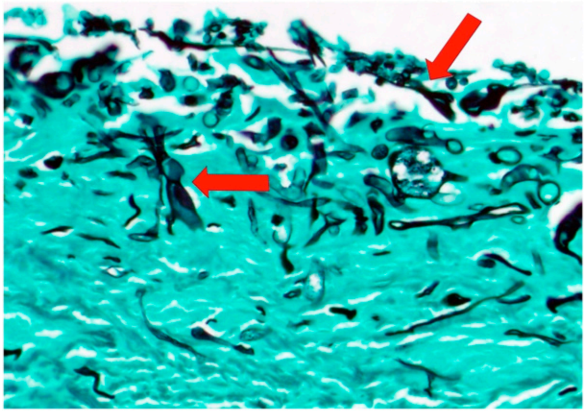

Figure 5. Grocott methenamine silver–stained histopathologic specimen of the infant's subcutaneous tissue demonstrating the *Rhizopus* species (red arrows).

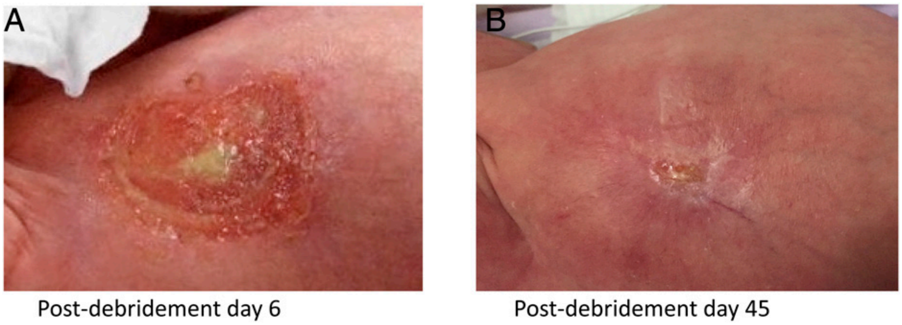

Figure 6. Infant's healing wound after surgical debridement.

WHAT THE EXPERTS SAY

Premature neonates are particularly vulnerable to opportunistic bacterial and fungal infections. When infants develop invasive fungal infections, *Candida* species are most commonly implicated. While uncommon, the zygomycosis family (formerly known as "mucormycosis") is a rare class of fungi involved in neonatal infections. Zygomycosis includes several organisms from the genera *Rhizopus, Mucor,* and *Absidia*. The organisms are typically transmitted through contact with contaminated surfaces such as wound dressings, adhesive tapes, IV catheters, and contaminated wooden tongue depressors. (1)(2)(3)(4)(5)(6) Risk factors for neonatal infection with *Rhizopus* include prematurity, extremely low birthweight, local skin trauma, exposure to broad-spectrum antibiotics, and/or corticosteroids. (1) A number of additional risk factors for invasive fungal infection are associated with populations outside the neonatal population; these include stem cell transplant recipients, patients with hematologic malignancies, diabetes, burns, and/or trauma. (7)

Neonatal zygomycotic infection can manifest as a cutaneous infection or, more commonly, as gastrointestinal disease with a presentation similar to that of necrotizing enterocolitis (NEC). However, presentation of NEC in this group is often atypical and lacks the radiographic changes typically seen with NEC. (8) This pattern is different in older children and adults who typically present with sinopulmonary and rhinocerebral patterns of infection. (1) The cutaneous form generally presents as a small discolored area that evolves as zygomycetes invade the surrounding vascular structures, creating a black, necrotic area with surrounding erythema. If untreated, the area will grow rapidly over the course of a few days as it did in this case.

Recognition of zygomycosis as a human pathogen has increased since 1990, with an overall mortality of 64% in neonates, and with 77% of the infected neonates being born prematurely. (1) Premature infants have immature immune systems that lead to an increased risk of disseminated disease and death, compared with the 56% mortality rate seen in pediatric patients. (1) Mortality rates vary by presentation, with a 38% mortality rate for infants with cutaneous *Rhizopus* infections, 78% for those with gastrointestinal infections, and 85% in infants with disseminated disease. (1)

Cutaneous fungal infections resulting from *Aspergillus, Mucor, or Rhizopus* species can mimic the necrotizing skin lesions found in a number of bacterial infections such as group A *Streptococcus, Clostridium perfringens, Escherichia coli, Bacillus anthracis,* and *Pseudomonas aeruginosa*. Unlike bacterial necrotizing fasciitis and gangrenous cellulitis, which can progress over the course of hours and cause rapid septic shock, fungal infections, including cutaneous *Rhizopus*, progress over the course of many days. Atypical infections such as herpes simplex virus and mycobacterium should also be considered.

The diagnosis of zygomycosis can be made through histopathology and/or culture, with a slight predominance of positive histopathology in 1 report (56% positive histopathology vs 44% culture positivity). (1) The histopathologic finding is hyphae with characteristic broad pauci-septate hyphae and branches occurring at right angles. The *Rhizopus* genus is the most commonly identified source of zygomycosis infections.

Early recognition of the infection with prompt surgical debridement and antifungal therapy can improve mortality, especially for infants with isolated cutaneous infections. The management of *Rhizopus* infections involves extensive surgical debridement and treatment with systemic amphotericin B (1–1.5 mg/kg per day). (9) Amphotericin is the first-line therapy for zygomycosis and other invasive fungal infections. Voriconazole and fluconazole have weak antifungal activity against *Rhizopus* species. (9) Kontoyiannis and Lewis recommend systemic antifungal treatment until the signs and symptoms are completely resolved and the patient's immune function has normalized, which can take weeks to months. (10)

Summary

- Zygomycosis is a rare, potentially life-threatening infection typically occurring in immunocompromised patients, particularly premature infants and neutropenic patients.
- Exposure to prolonged broad-spectrum antibiotics, steroid therapy, and a humidified environment makes premature infants particularly vulnerable to fungal infection. Invasive vascular access and adhesive dressings further damage their fragile skin integrity, which becomes a potential site for inoculation and infection.
- Aggressive skin care and thorough daily skin exams are vital to the overall health of preterm infants. In the event of skin findings concerning for fungal infection, prompt management with antifungals and/or surgical debridement can improve survival.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical manifestations and diagnostic features of neonatal fungal infections.
- Know the treatment and complications of neonatal fungal infections.

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ANSWER KEY FOR SEPTEMBER 2018 NEOREVIEWS

Neonatal Antibiotic Use: What Are We Doing and Where Shall We Go? 1. C; 2. D; 3. D; 4. A; 5. E.

NICU Communication: The Many Disguises of Opportunity: 1. C; 2. D; 3. A; 4. D; 5. A.

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Answer Key appears on page e619.

Advanced Technology and High Sensibility in Providing Safe Neonatal Care in Intensive Care Units

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Education Gaps

Clinicians need to recognize that the main causes of medical errors are related to complex systems and human fallibility. However, providers have alternatives to avoid errors, by creating better coordinated systems, improving reliability, and granting special attention to human factors engineering.

Abstract

Possibly no other field of medicine has undergone such dramatic progress in reducing mortality and morbidity as the care of preterm newborns. In recent years, remarkable advances in the care of pregnant women and their children have led to an increase in infant survival. However, advances in neonatal care need to be accompanied by mechanisms that help us deliver care safely to this most vulnerable population.

Objectives

After completing this article, readers should be able to:

1. Recognize that patient safety is a top priority in medicine.
2. Review reasons for the occurrence of errors in the NICU and describe strategies to prevent these errors.
3. Explain the importance of individualized developmental care and assessment in the NICU.
4. Describe how to educate future leaders about patient safety.

PATIENT SAFETY: THE MORAL COMPASS

As defined by Sir Liam Donaldson, envoy of the World Health Organization (WHO), safe patient care involves performing the right action for the right person at the right time and in the right place, and avoiding adverse events. Adverse outcomes are outcomes that occur as a result of actions (or lack of actions) by the medical team rather than due to patient illness. As stated by Sir Liam Donaldson: *"To err is human, to cover up is unforgivable, and to fail to learn is inexcusable."*

AUTHOR DISCLOSURE Dr Martinez has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

The technical skills and complexity of medical practice have grown significantly over the years; however, these same technologies, medications, and life saving surgeries can potentially cause harm to patients, and the next generation of health-care providers should be taught how to prevent injury. (1)(2) Physicians rely on the support of medical care systems (which are often very complex) to enable them to carry out their tasks. However, errors can occur during each stage of patient care.

Harm to patients is not absolutely unavoidable, but can and must be prevented. Therefore, measures to promote patient safety are crucial. To achieve this goal, systems, institutions, physicians, and other allied health-care personnel must learn from past errors and learn how to avoid them in the future. Clinicians have to adapt their work flow to achieve safe health care, which should be a fundamental and achievable goal.

People who work in health care are privileged to be in a field that cares for human beings, reduces suffering, and saves lives. This care does not always produce results according to the plan, and sometimes causes suffering, impairments, and/or deaths. Medical errors can result in injury to patients, which are both physical and psychological, and can unfortunately be lifelong in some instances. Not all "costs" can be quantified; in addition to the financial costs, medical errors have an important cost in terms of loss of confidence in the medical system, decrease in patient satisfaction, and potential physician dissatisfaction with their professional work. The difficulties in managing and implementing health-care systems also contribute to suboptimal conditions for the development of safety programs, and sometimes become a hindrance in developing safe medical practices.

It is important to determine the causes of adverse events as well as potential methods of reducing their occurrence by performing a root cause analysis. As defined by the Institute of Safe Medication Practices Canada, a root cause analysis is “a systematic process of investigating a critical incident or an adverse outcome to determine the multiple, underlying contributing factors. The analysis focuses on identifying the latent conditions that underlie variation in performance and, if applicable, developing recommendations for improvements to decrease the likelihood of a similar incident in the future.” (3) The State Claims Agency suggests that this analysis “can provide a retrospective review of a patient safety incident to identify what, how, and why it happened. The analysis is then used to identify areas for change, recommendations, and sustainable solutions to help [minimize the recurrence] of the incident type in the future.” (4)

As Dr Frank Morris emphasizes (5), adverse medical events are not uncommon during the care of preterm infants in the NICU. It is important to determine the causes of these events, as well as identify potential methods to reduce their occurrence. Both human fallibility as well as the complex organization of the medical system in the NICU are major contributors of errors related to attention. Preterm newborns in the NICU are especially fragile and are subject to multiple interventions.

The environment in the NICU is often chaotic, with multiple admissions, often unscheduled, of unstable patients. Health-care clinicians in NICUs, therefore, face multiple urgent problems at the same time, and their tasks are frequently interrupted. Intensive care must be performed accurately throughout the day; thus, it is essential that the hand off of each newborn’s care from one team to the next be accurate and strictly controlled. Each shift change is an occasion that can give rise to errors due to a failure to implement planned actions. Simplifying steps during clinical practice and thereby decreasing the need for problem-solving can potentially decrease the chance of errors. Streamlining can include decreasing the need for multiple steps of data entry.

Injury suffered by preterm infants is sometimes not as evident as that noted in older children or adult patients. One of the most common adverse events associated with preterm infants are nosocomial infections, but complications related to intravascular catheters and accidental extubations also occur. Indirect hyperbilirubinemia is an extremely frequent issue in the premature infant and it is important to manage this complication in a timely manner. (6) Preventable adverse events as a result of errors associated with the indication for medications as well as actual medication administration are also observed in the NICU setting.

Dr Frank Morris also suggests that most medical errors occur because humans simply cannot perform all expected tasks perfectly at all times. (5) Research estimates that humans have a short period of immediate memory for only 7 items, that the minimum attainable rate for default errors is 1 per 100 tasks, and that the minimum attainable rate for errors per commission is 3 per 1,000 tasks. Multiplying the number of tasks required for the care of a preterm newborn hospitalized for several months in the NICU by those error rates and then by the number of patients in the NICU during that time gives us an estimate of probable errors over that period. This total will very quickly reach a very high number of errors, many of which have the potential to harm a patient.

PREVENTION OF MEDICAL ERRORS

WHO states that to prevent errors in medicine, basic strategies must be pursued: (7)

- Providers must identify human behavioral factors responsible for errors, and redesign the work flow in NICUs to minimize errors.
- Providers must designate and employ reliable systems that prevent errors or block them before they reach the patient.

In practice, there is a critical and repeated interaction between these strategies. In addition, information technology specialists can design systems to avoid human error, such as software systems for medication order entry and indications for medication use. However, these specialists must also observe how prescribers actually use or misuse the system to identify new opportunities for error that are inadvertently created. Process reliability can be improved by decreasing the number of consecutive steps or by increasing the reliability of individual steps. Dr Frank Morris also emphasizes (5) that high-reliability organizations are characterized as those that exhibit a state of mindfulness about potential error and are constantly concerned about:

- Identifying errors
- Dedicating time to observe workers performing tasks
- Training workers to perform skills using the best approaches
- Enabling workers to identify and solve problems

In October 1846, after women in a maternity hospital died despite receiving care from physicians, Dr Ignaz Semmelweis thought that the cause of the deaths could be related to the hands of physicians who came to the hospital after working in the morgues. Based on this hypothesis, he decided to implement a handwashing lavatory for physicians for the first time in medical history. Initially, his idea was criticized, but after some years, it was officially implemented.

Proper handwashing is, and must be emphasized as, the most important action (in spite of being a very old proposal) for decreasing nosocomial infections in the NICU. Proper handwashing must be practiced consistently and with the same technique by all team members, as the pioneer Dr Semmelweis tried to implement more than 150 years ago.

MEDICATION ERRORS

The WHO publication “Medication without harm: third global patient safety challenge” summarizes that “unsafe medication practices and medication errors are a leading cause of avoidable harm in health-care systems across the world. Medication errors occur when weak medication systems and/or human factors (such as fatigue, poor environmental conditions, or staff shortages) affect prescribing, transcribing, dispensing, administration, and monitoring practices. These errors can then result in severe harm, disability, and even death. Although errors occur most frequently during administration, there are risks at different stages of the medication process.” (8) WHO provides a list of several types of medication errors. (9)

Types of Errors

- Dosage problems or incorrect dosage
- Prescription errors
- Missing or incorrect weight
- Prescribing policies not followed
- Medication omissions
- Absent or wrong prescription date
- Drug/drug interaction; medication given to known allergic patient; medication duplication

The process of administering a medication is a complex one that involves a system with many sequential steps developed by multiple people, and each step is subject to human error. Hospitals must focus their attention on information technology systems, but also on the human factors that are involved. The following list provides recommendations for avoiding errors related to medication administration:

- Standard concentrations for infusion
- Order sets or preprinted orders
- Avoidance of the use of dangerous abbreviations
- “TALLman" lettering for drugs that have lookalike names to call attention to the critical differences
- Removal of certain high-alert drugs from "ward stock" and requiring dispensing only by the pharmacy
- Restriction of verbal orders to emergency situations
- Requirement for double-checking by a second professional at each step of the medication process
- Special color-coded labels for high-alert medications
- Storage of high-alert medications separately from other drugs in each location where drugs are stored, including the NICU
- Labels on infusion pumps that list the name of a high-alert drug being infused
- Requirement for handoff verification checks from one caregiver to the next for a patient receiving a high-alert drug infusion (5)

VENTILATION STRATEGIES

The main objective of having different ventilation strategies is to achieve the least degree of lung injury while achieving adequate lung function. It is, however, difficult to assess the superiority of any specific ventilation strategy over others. If neonatologists use specific ventilation strategies and/or ventilators with which they are not familiar, this can lead to increased errors, with subsequent higher risk of pulmonary injury. A weakness of current studies is the difficulty of evaluating and comparing the ability of the operators in using different strategies of respiratory assistance. Promoting research in this area is necessary to determine the best ventilator strategies, with less possibility of errors in its application by different operators. (8)(9)(10)

FATIGUE AND HUMAN ERROR

Fatigue is an important aspect of human fallibility that contributes to the occurrence of adverse events. The probability of an error increases with clinician fatigue and decreases when the clinician has an opportunity to rest. Parshuram (11) has described 4 sources of fatigue in health-care staff:

- Acute sleep deprivation
- Accumulated sleep debt
- Work overload and physical exhaustion
- Circadian rhythm disruption

Clinician fatigue leads to a decrease in performance and an increase in the risk of error and adverse events. Dawson and Reid (12) compared the psychomotor cognitive performance of 40 individuals under 2 separate conditions: 1) staying awake for 28 hours, and 2) drinking alcohol at intervals until the blood alcohol concentration reached 0.10%. Using a computer-assisted eye-hand coordination test at 30-minute intervals, the researchers plotted the performance decline on the test as a percentage of the initial performance in each condition. Similar decreases in performance were observed after sustained wakefulness and ingestion of alcohol.

After 17 hours of sustained waking, the performance was equivalent to that demonstrated by a person who had a blood alcohol concentration of 0.05%; after 24 hours of waking, the cognitive psychomotor performance was similar to that observed when the concentration of alcohol in the blood was 0.10% (an individual impaired by alcohol to this degree would not be allowed to operate a motor vehicle, but is allowed to care for a patient). A meta-analysis of 60 studies concluded that lack of sleep reduced overall physician performance by more than 1 standard deviation and significantly increased error rates.

STRESS AND PERFORMANCE

Psychologists Robert Yerkes and John Dodson created the inverted-U model (also called the *Yerkes-Dodson law*) in 1908. (13) This model shows the relationship between stress and performance (Fig). Based on this model, maximal performance is obtained when people experience a moderate level of stress. If people have a task associated with minimal stress, they are often bored and have no incentive to put more effort into the task, leading to a decline in performance (left side of the graph). However, extremely high stress (right side of the graph) can be associated with high anxiety, which is associated with poor performance. Ideally, if the task is associated with a midlevel stress, the performance is optimal (middle of the graph).

FAILURE IN COMMUNICATION

Shortening physician work hours to reduce the risk of error in a NICU requires a greater number of physicians and more frequent physician shifts, resulting in an increased number of handoffs. Streitenberger and collaborators (14) recommend the following strategies to improve the quality and accuracy of information provided during handoffs:

- Standardize and simplify the process using a checklist
- Avoid/minimize interruptions
- Limit the use of intermediate persons performing the handoffs
- Use a common communication style
- Implement a restating/relistening process
- Maintain patient-centered communication

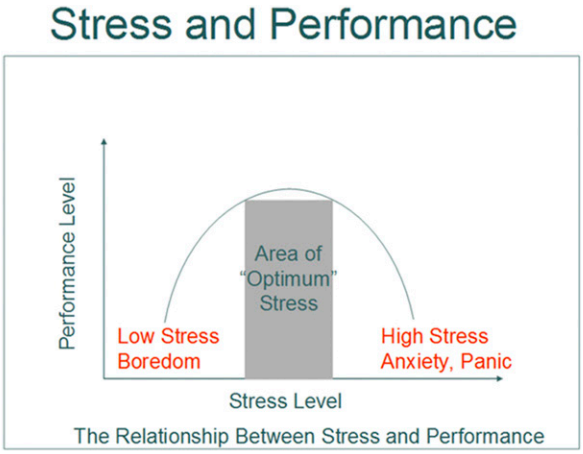

Figure. The inverted-U model showing the relationship between stress and performance. Reprinted with permission from Yerkes RM, Dodson JD. The relation of strength of stimulus to rapidity of habit-formation. *J Comparative Neurol Psychol.* 1908;18:459–482

Another approach for establishing safer medical communication is described in detail by Catchpole and colleagues. (15) To improve handoffs by the surgical team to the ICU staff after cardiac surgery in infants, this group adapted the methodology of the support team in the pit stop of Formula 1 cars and aviation models. The researchers visited a Formula 1 team to observe pit-stop practice sessions and then developed new handoff practices for anesthetists, surgeons, intensivists, and nurses by incorporating safety measures learned from the work of the pit-stop crew. These included:

- Leadership in conducting the practice
- Planning according to special requirements
- Definition of sequence of tasks
- Assignment of tasks according to team skills
- Discipline in the execution of tasks
- Checklists of testing

The investigators reported reductions in technical errors, information failures, and time required to perform tasks.

INDIVIDUALIZED DEVELOPMENTAL CARE AND ASSESSMENT

Better understanding of the role of early sensory experience and environmental influences leads to a new goal in NICUs, which is the survival of infants without disabilities while also preserving their full potential. Attention must focus on the role of chronic stress of infants receiving intensive care. Repetitive painful procedures as well as early experiences of overstimulation or inadequate stimulation during early life can alter the programming of the hypothalamic hypophyseal adrenal axis, thus increasing the risk of developing cardiovascular disease, hypertension, and glucose intolerance later in life.

Individualized developmental care, as proposed by Heidelise Als, (16) is based on the infant's degree of maturity, and aims at reducing stress and promoting physiologic stability in preterm infants. The most important interventions to reinforce positive outcomes must be those that not only have immediate direct effects, but continue to have an impact even after discharge. Stimulation of the interaction between a mother and her child and the mother-child bond in the early stages of life likely has long-term effects. It is unlikely that a single intervention, though effective, will achieve the well-being of preterm newborns and their families, because health difficulties in these infants are multifactorial, as suggested by Als. (16) The design of future studies must account for all of these factors to obtain real and convincing evidence about the benefits of specific therapies.

The medical actions that lead to actual advances must be programmed according to the contemporary sociocultural context, and guided by moral and ethical principles from which clinicians must never depart. In del Salvador University, Buenos Aires, Argentina, I spearheaded a Special Prevention and Anticipatory Program called "An Invitation to Life," which is based on educating parents and expectant parents. (17) This program provides families and pediatric health-care professionals with a summary of recent advances in science, how to see the world through the eyes of children, and how childhood memories persist and could diminish or increase stress levels. This program encourages and leads parents and pediatric health-care clinicians to modify their goals and try to optimize results.

Clinicians in NICUs have the remarkable opportunity of participating in the dream of a new beginning alongside parents of premature infants, accompanying families to find a new perspective in their lives, to increase their self-esteem, and to have faith in their own strength. (18) The philosophy of any parenting program for premature infants should be based on the belief that physicians do not always know what parents need. Rather, physicians should humbly listen to parents, creating a climate where parents truly *feel* that clinicians are interested in them as people and not as numbers, and that their emotions and feelings are important. This will enable parents to willingly share their feelings (stresses, frustrations, and joys) and needs with clinicians so that families can receive appropriate help and support. Clinicians need to learn what families really feel, what families do NOT want clinicians to do, as well as what they are hoping clinicians would have *done* but never did. (17) Actions to promote human values include the following (1)(2):

- Actively encourage parents of preterm newborns and medical staff to share information
- Show empathy, honesty, and respect
- Communicate clearly and precisely
- Develop the ability to listen permanently
- Obtain informed consent for clinician actions
- Show respect for each patient's differences
- Pay attention to the patients' perceptions of reality and their individual needs
- Invite parents to discuss details and meet their gaze
- Explore emotions and deliver empathy
- Coordinate these steps to follow with parents and their family

This approach can lead to several benefits including, as noted by WHO: "Patients who know what to expect can help identify potential incidents before they occur. Telling a patient story can allow reflections that are not based on statistical reports."(7)

Responding to patient safety incidents is an ethical and moral imperative for physicians and other health-care professionals. The appropriate response to a patient safety incident and/or medical error is not easy, but must include a blame-free environment and the corrective action must be incorporated into routine medical care. Emphasizing a policy of permanent transparency is an important goal for medicine. Furthermore, the ability to learn quickly from mistakes, respond appropriately, and modify practices based on research to improve safety and quality in the care of patients is critical. The culture of safety must clearly replace the old culture of guilt, which only engenders shame and walls of silence. (18)

THE SEVEN PILLARS

The University of Illinois has outlined the guiding principles for behaviors that foster safe care of patients. This approach is called the "Seven Pillars" (19) and is an excellent tool to implement a safe and just culture in medicine; it consists of the following:

1. Report of incidents
2. Investigation
3. Communication and information
4. Apologies and repair
5. Improvements in the system
6. Data tracking
7. Education and training

Working as a team means that individual needs must conform with those of the group, resulting in a positive emotional balance. In addition, clinicians must learn how to substitute roles and to appreciate the perspectives of others.

EDUCATING FUTURE LEADERS ABOUT PATIENT SAFETY

Students/trainees in the health science field are extremely vulnerable during the first years of their learning period. If the concepts of patient safety outlined in this review are introduced early, the culture of patient safety can improve dramatically. The WHO multiprofessional medical school curriculum (2) is an important step forward to assist with this approach. However, this is not the only priority. At present, hospital systems are sometimes poorly designed to prevent and/or manage medical errors. We must consider some proactive strategies to help the next generation of clinicians be prepared, some of which are highlighted below:

- Motivation: Help students realize that they are a critical part of instituting a culture shift in patient safety
- Positive attitude: Encourage students to apply the best of the old system in addition to creating new processes
- Anticipation of slow changes: Implementing new approaches and innovations is often associated with an initial period of uncertainty and doubt but it is important to persist toward the goal
- Focus on both the microsystem and macrosystem: This bilevel approach is critical for effective and sustaining change

Clinicians need to recognize early in their career that while advances such as new drugs and new technology can help to provide more effective care, reducing the risk of adverse events is the most important action to improve patient safety. While human mistakes may be impossible to eliminate completely, students need to be taught that prevention of errors is a priority. An important guiding principle for students and trainees is that patient safety involves doing the right thing, based on evidence, in the right moment, for the right person, and honestly learning from mistakes and permanently stimulating proactive approaches. Patient safety is the responsibility of all clinicians with different degrees of responsibility, who together should develop strategies that lead to improvements. To progress, safety needs to rely on human factors engineering and systems, as well as incorporate strategies from other disciplines such as aviation and nuclear medicine. It is a top priority to maintain a balance between high technology and high sensibility when providing medical care.

At our Institute of Safety and Quality in Health Sciences at del Salvador University, Argentina, we initiated connections with other disciplines in health care to implement teaching and learning activities focused on understanding how teamwork is effective and organized appropriately. In the School of Medicine, we have developed an official program of patient safety for medical students, which lasts from the first to the last year of their curricula, with a pedagogical design based on the WHO patient safety curriculum guide. The goal is to create future leaders on safety by introducing this young audience to realistic scenarios.

As noted by Sir Liam Donaldson during his presentations: "Years after the Institute of Medicine report we are still struggling as a global community [about] how to explain to patients and families if health care is safe." This is because it is difficult to measure baseline patient safety and quantify improvements. Fortunately, the field of patient safety is maturing. Proof of this is that students are being trained in safety; clinicians and researchers are designing interventions; health-care systems are implementing programs; regulators are evaluating practices; governments are launching national agencies, and the WHO is implementing safety projects with international partners. Collectively, this is a significant effort, but there is limited evidence that patient safety results have improved. We have learned that there are no quick solutions.

Looking ahead, we need to define scores with valid measurements guided by science and make a commitment to work together. We must teach clinicians how to standardize data collection with strict quality control, and it is essential to collect data in multiple sites. The challenge that health-care systems face is to ensure that patient safety is at the heart of how we think, how we work, and how we educate so that it is deeply incorporated into medical organizations.

CONCLUSION

> *"It may be part of human nature to err, but it must also be part of human nature to create solutions, find better alternatives and face the challenges ahead."* (20)

Great progress has been made in neonatal care, but the health-care system must do much more. Clinicians must consider a priority those changes that, because of their efficiency, have long-term relevance and are applicable anywhere in the world without any limitations. The health-care system faces a great challenge, the era of reflection between real progress and innovations (ie, what we are doing and what we should actually do). This new paradigm needs to be adopted universally.

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American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the issues in the organization of perinatal care (eg, regionalization, transport, practice guidelines, benchmarking data, quality improvement).

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Diagnosing and Managing Hirschsprung Disease in the Newborn

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Education Gaps

1. It is important for clinicians to be aware that Hirschsprung disease can be present despite the passage of meconium within the first 48 hours after birth.
2. Even after successful pull-through surgery, patients with Hirschsprung disease remain at risk for constipation, fecal incontinence, enterocolitis, and decreased quality of life.

Abstract

Hirschsprung disease is characterized by the absence of enteric ganglia in the distal bowel and is caused by the failure of enteric neural crest–derived cells to complete their craniocaudal migration along the intestine during embryogenesis. Neonates typically present with failure to pass meconium within the first 48 hours after birth. Diagnosis relies on rectal biopsy to document the presence of aganglionosis, and management requires surgical resection of the aganglionic segment. Despite advances in the diagnosis and management of the disease, patients remain at risk for long-term gastrointestinal morbidity, including obstructive symptoms, fecal incontinence, and enterocolitis, with negative implications on quality of life. Neuronal stem cell–based therapy is being explored as a novel treatment for this disease.

Objectives

After completing this article, readers should be able to:

1. Identify the clinical presentation of Hirschsprung disease.
2. Describe the preoperative management of neonates with Hirschsprung disease.
3. Discuss the signs and symptoms of Hirschsprung-associated enterocolitis.
4. Recognize the potential postoperative complications and be familiar with their management.
5. Explain the long-term impact of Hirschsprung disease on a patient's quality of life.

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ABBREVIATIONS

AChE	acetylcholinesterase
ARM	anorectal manometry
ENS	enteric nervous system
H&E	hematoxylin and eosin
HAEC	Hirschsprung-associated enterocolitis
HAPC	high-amplitude propagating contraction
HSCR	Hirschsprung disease
RAIR	rectoanal inhibitory reflex

INTRODUCTION

Hirschsprung disease (HSCR) was first described by Harald Hirschsprung in 1886, but the pathophysiology of the disease was poorly understood until the 1940s. At that time, Orvar Swenson identified the absence of ganglion cells in the contracted and functionally obstructed distal colon of affected patients. He concluded that resecting the aganglionic segment was the treatment of choice and performed the first successful pull-through procedure in 1948. (1) Over the course of the next 2 decades, Orvar Swenson, Bernard Duhamel, and Franco Soave developed the surgical approaches most commonly used today. (2) While the treatment of HSCR requires surgical resection of the aganglionic segment, early diagnosis and prompt initiation of medical therapy are essential. Neonatologists and other pediatric providers must therefore be familiar with HSCR and maintain a high index of suspicion for its diagnosis to reduce the risk of complications associated with this disease. This review will highlight the pathophysiology, clinical presentation, diagnosis, and management of HSCR.

EPIDEMIOLOGY

HSCR occurs in 1 in 5,000 live births and is the most common congenital neurointestinal disease. (3)(4) The incidence varies among ethnicities: 1 in 10,000 Hispanics, 1.5 in 10,000 whites, 2.1 in 10,000 blacks, and 2.8 in 10,000 Asians. (5) In 90% of cases, HSCR presents in the newborn period. The remainder of affected patients present later in life, sometimes during adolescence or adulthood, though this has decreased in frequency with growing awareness of the disease.

HSCR is characterized by intestinal aganglionosis that begins at the distal end of the bowel and extends proximally for variable distances. The most common form, referred to as "short-segment Hirschsprung disease," affects 80% of patients, and is limited to the rectosigmoid. In long-segment disease, the aganglionosis extends proximal to the sigmoid colon, with total colonic aganglionosis occurring in 5% of cases, (6) often extending into the terminal ileum. Approximately 1% of patients have total intestinal aganglionosis that involves both the small and large intestine. Males predominate among patients with short-segment HSCR, with a male-to-female ratio of 4:1, (7)(8) while long-segment aganglionosis affects the sexes equally.

PATHOPHYSIOLOGY

HSCR is a congenital disease of the enteric nervous system (ENS), which refers to the complex neuronal network present in the wall of the gastrointestinal tract. The ENS is the intrinsic innervation of the gut, capable of autonomous function in the absence of central nervous system input. It controls many aspects of gut function, including motility, sensation, absorption, secretion, barrier integrity, and immunity. (9) The ENS arises embryologically from neural crest cells that delaminate from the dorsal neural tube and migrate to the foregut at about week 4 of human development. These cells migrate craniocaudally to populate the entire length of the gastrointestinal tract by week 7, (10) forming a pattern of 2 concentric rings of interconnected enteric ganglia, referred to as the *submucosal* (Meissner) and *myenteric* (Auerbach) plexuses. HSCR results from the failure of these cells to complete their migration, leaving the distal end of the gut aganglionic and consequently functionally obstructed.

The underlying cause of HSCR primarily appears to be abnormalities in the proliferation, migration, and differentiation of the enteric neural crest–derived cells. Studies in avian and rodent embryos have shown that insufficient cell proliferation or survival, delayed cell migration, and premature neuronal differentiation can all contribute to the early termination of cell migration and failure of the enteric neural crest–derived cells to reach the distal end of the bowel. (11) The resulting aganglionic segment becomes contracted, likely because of unbalanced innervation from the extrinsic nervous system, which is primarily cholinergic and therefore excitatory. The aganglionic segment results in a functional obstruction, with the characteristic development of "megacolon" proximal to it.

HSCR has a complex, non-mendelian inheritance pattern that is further complicated by variable penetrance and incomplete phenotypic expression. (12) Currently, 11 genes have been found to be associated with human HSCR. Most important among these is *RET*, a receptor tyrosine kinase present on enteric neural crest–derived cells and required for their survival, proliferation, migration, and differentiation. Nearly all patients have a coding or noncoding mutation in the *RET* gene. Other genes associated with the disease are shown in Table 1. (13)

Most cases of HSCR are sporadic, with approximately 20% being familial. (14) Familial cases are more often associated with long-segment disease and identification of a coding sequence mutation in *RET*. Several genetic syndromes are also associated with HSCR. The most common among these is trisomy 21, which affects 10% of all children with HSCR. Another 30% of HSCR cases are associated with other syndromes (Table 2). (14)

TABLE 1. **Genes Associated with Hirschsprung Disease**

GENE SYMBOL	PROTEIN ENCODED	FUNCTION
RET	Ret proto-oncogene	Tyrosine kinase receptor expressed on ENCCs, regulates their survival, proliferation, migration, differentiation
GDNF	Glial cell-derived neurotrophic factor	Ligand for *RET*
NRTN	Neurturin	Ligand for *RET*
ECE1	Endothelin-converting enzyme 1	Cleaves *EDN3* precursor to biologically active peptide
EDNRB	Endothelin receptor type B	G protein coupled receptor expression on ENCC derived cells, regulates their proliferation and differentiation
EDN3	Endothelin 3	Ligand for *EDNRB*
NRG1	Neuregulin 1	Cell adhesion molecule, involved in cell-cell signaling during development
SOX10	SRY-box 10	Transcription factor involved in ENCC development
PHOX2B	Paired like homeobox 2b	Transcription factor expressed by ENCCs
ZEB2 (SIP1; ZFHX1B)	Zinc finger E-box binding homeobox 2	Encodes Smad-interacting protein 1
KIF1BP (KIAA1279; KBP)	KIF1 binding protein	Interacts with actin and microtubule cytoskeleton

ENCC=enteric neural crest cell.

DIAGNOSIS

Failure of a full-term infant to pass meconium within 48 hours should raise concern for HSCR. In a landmark article in 1955, Sherry and Kramer reported that 94% of full-term infants will pass stool within the first 24 hours after birth, and 99.8% will pass a stool within 48 hours. (15) Among newborns with HSCR, only 6% pass meconium by 24 hours, but 37% to 54% will pass meconium by 48 hours. (16)(17) Therefore, while the failure to pass meconium within 48 hours after birth should certainly raise concern for HSCR, the passage of stool does not rule out the disease.

In addition to the delayed passage of meconium, other important clinical signs of HSCR in neonates include abdominal distention, bilious or nonbilious emesis, feeding difficulty, and rarely, pneumoperitoneum or signs of peritonitis. Importantly, approximately 10% to 24% of children with HSCR will present with explosive diarrhea, often with abdominal distention, vomiting, or fever, suggestive of the diagnosis of Hirschsprung-associated enterocolitis (HAEC). (18)(19)(20)(21) HAEC can occur as the presenting feature of HSCR or it can occur after a definitive diagnosis has been made, either before or after pull-through surgery. Clinicians must therefore maintain a high index of suspicion for a diagnosis of HSCR, even when a patient presents with diarrhea.

When confronted with a newborn with obstipation, the neonatologist must consider other possible diagnoses in addition to HSCR. These include meconium plug syndrome, small left colon syndrome, meconium ileus, anorectal malformation, and colorectal atresia. A detailed

TABLE 2. **Syndromes Associated with Hirschsprung Disease**

SYNDROME	GENETIC ABNORMALITY	PHENOTYPE
Shah-Waardenburg	*SOX10, EDNRB, EDN3*	HSCR, hair/skin/eyes hypopigmentation, and congenital hearing loss
Haddad	*PHOX2B*	HSCR and Congenital Central Hypoventilation Syndrome
Mowat-Wilson	*ZFHX1B*	HSCR, mental retardation, epilepsy, and delayed motor development
Goldberg-Shprintzen	*KIAA1279/KBP*	HSCR, microcephaly, mental retardation, polymicrogyria
Down syndrome	Trisomy 21	Facial dysmorphism, intellectual disability, multiple congenital anomalies

physical examination should therefore include assessment of the presence, position, and size of the anus, as well as evaluation for syndromic features (Table 2). If clinical suspicion for HSCR persists, then a contrast enema, typically with water-soluble contrast, is recommended. The diagnosis of a meconium plug or small left colon on contrast study does not exclude HSCR, because both of these conditions can be associated with HSCR. (22)(23)

HSCR has several characteristic features on contrast enema. A classic finding is reversal of the rectosigmoid ratio. Normally, the diameter of the rectum is about equal to the diameter of the sigmoid colon. When the rectosigmoid ratio is less than 1, suspicion for HSCR is increased. Another feature is presence of a transition zone, which is seen as an abrupt caliber change between proximal dilated colon and a narrow distal colon/rectum. (24) Finally, a sawtooth or spiculated appearance to the rectal mucosa also raises suspicion. A characteristic contrast enema in a newborn with HSCR is shown in the Fig.

It is important, however, to note that radiographic abnormalities may be absent in newborns because of their young age and an insufficient amount of time for proximal bowel dilation to occur. In a recent study of contrast enemas in neonates with HSCR, 75% had an abnormal rectosigmoid ratio, 85% had a transition zone, and only 50% had mucosal spiculations. (25) Importantly, even when a transition zone is present, the contrast enema cannot reliably predict the length of aganglionosis, especially in cases of long-segment HSCR, for which the sensitivity of contrast enema has been reported at just 62.5%, compared with 91.7% for patients with short segment disease. (26) When suspicion for HSCR is raised with findings on contrast enema, additional evaluation is needed to confirm the diagnosis.

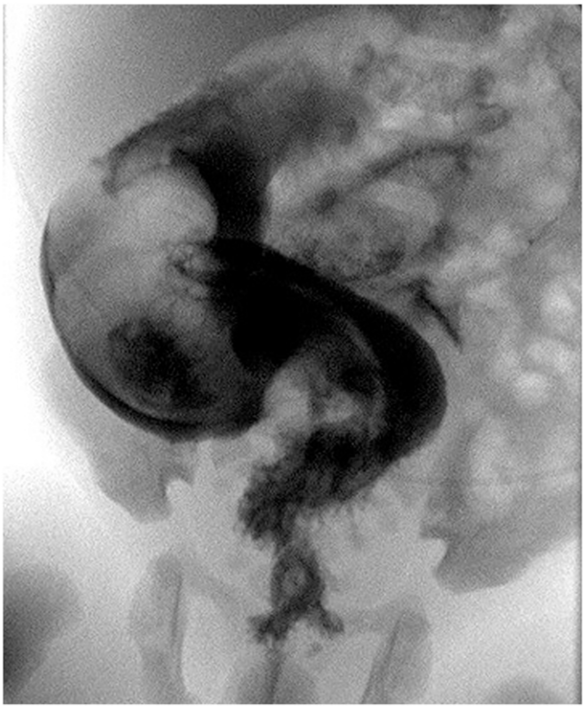

Figure. Contrast enema was performed in an otherwise healthy 2-day-old full-term male infant with abdominal distention and failure to pass meconium. The enema shows an abnormal rectosigmoid ratio, with a transition zone in the distal sigmoid colon. The rectum also demonstrates a sawtooth mucosal pattern. These features are highly suggestive of Hirschsprung disease.

The gold standard for diagnosing HSCR is a rectal biopsy for histologic confirmation of the absence of ganglion cells in the distal rectum. Dr Swenson made this seminal observation when he described the usefulness of rectal biopsy for the diagnosis of the disease. (27) Full-thickness rectal biopsy was most often used for diagnosis until the mid-1960s, when Dobbins and Bill demonstrated that ganglion cells could be reliably and consistently seen on suction rectal biopsy samples. (28) Currently, 80% of physicians worldwide rely on suction biopsy for diagnosing HSCR. (29) The benefits of this technique are that it can be performed at the bedside without anesthesia, it is associated with minimal pain, and there is no need for suturing of the biopsy site. One disadvantage of a suction rectal biopsy is the small sample size in comparison with a full-thickness biopsy specimen. However, as long as sufficient submucosa is included in the sample, the submucosal plexus can be examined using hematoxylin and eosin (H&E) staining. The pathologist generally scans 50 to 100 histologic sections to confirm the absence of ganglion cells. The presence of hypertrophic nerve fibers, which are derived from the extrinsic innervation to the gut, in the lamina propria, is associated with HSCR. (29) In some centers, acetylcholinesterase (AChE) staining continues to be used as an adjunct to H&E staining, with the presence of significantly thicker and denser AChE-positive nerve fibers, particularly in the muscularis mucosae, supporting the diagnosis of HSCR. (30)(31) However, AChE staining requires frozen tissue, is technically challenging, and is associated with significant interobserver variability in interpretation. Over the past several years, it has been replaced at many centers by calretinin immunostaining, which is a more reliable stain that can be performed on formalin-fixed, paraffin-embedded tissue. The absence of calretinin in the lamina propria is diagnostic for HSCR. (31)(32)

Another adjunctive diagnostic test that can be considered in patients suspected of having HSCR is anorectal manometry (ARM). Normally, rectal distention with a balloon leads to reflex relaxation of the internal anal sphincter, a phenomenon referred to as the *rectoanal inhibitory reflex* (RAIR). In patients with HSCR, the RAIR is absent. (33) Children with severe constipation can avoid an unnecessary rectal biopsy by undergoing ARM and demonstrating a normal RAIR. (3) The age at which this test may be considered is controversial, with some authors suggesting that neonates may not exhibit the RAIR as a result of physiologic immaturity of anorectal function. However, a systematic review of diagnostic tests used for HSCR included a subset analysis in this age group and found that the sensitivity of ARM in infants younger than 6 months was 88%, compared with the total group sensitivity of 91%, suggesting that even in infants younger than 6 months, this test may be beneficial. Furthermore, Benninga et al and de Lorijn et al showed that term and premature infants older than 26 weeks' postmenstrual age have a well-developed RAIR upon rectal distention and thus would be able to undergo ARM for diagnosis. (34)(35)

HSCR remains a disease that requires a high index of clinical suspicion to ensure timely diagnosis, thereby minimizing the risk of morbid complications such as HAEC or intestinal perforation. Clinicians must remain vigilant in the evaluation of neonates who fail to pass meconium within the first 48 hours after birth, while keeping in mind that up to 54% of children with HSCR will still pass meconium normally. Thus, even if the infant passes meconium before 48 hours, the clinical findings of abdominal distention, bilious or nonbilious vomiting, and feeding difficulty should prompt the clinician at least to consider the diagnosis of HSCR.

PREOPERATIVE CLINICAL MANAGEMENT

Once the diagnosis of HSCR is histologically confirmed, initial management includes anal dilations and/or rectal washouts to evacuate stool, decompress the colon/rectum, and minimize fecal stasis, which increases a neonate's risk of developing HAEC. (36) Colonic decompression is also important because it avoids excessive colonic dilation, which complicates the pull-through procedure and can adversely affect postoperative colonic function. Anal dilations are often sufficient to promote evacuation in children with short-segment HSCR by gently stretching the anal sphincter. These are performed once or twice daily using an appropriately sized dilator. Anal dilations should be delayed 24 hours after rectal biopsy to minimize risk of rectal injury.

If dilations do not effectively evacuate the colon, once- or twice-daily rectal irrigations should be initiated. These are performed using a flexible rectal catheter with repeated instillation of 20 to 30 mL of saline until the effluent is clear. (37) In long-segment HSCR, especially when the aganglionosis extends proximal to the splenic flexure, irrigations are often inadequate to evacuate the colon and these patients may need to undergo a diverting ostomy. In this procedure, with the administration of general anesthesia, the surgeon performs serial biopsies with frozen section analysis conducted by an experienced pathologist until the level of normally ganglionated bowel is identified. A colostomy or ileostomy is performed at that level, hence the name *leveling ostomy*.

If the infant has signs or symptoms of HAEC, including explosive diarrhea, abdominal distention, lethargy, fever, or sepsis, treatment needs to be initiated promptly, because HAEC is the most common cause of death from HSCR. (38)(39)(40) Clinicians and parents need to be aware of this diagnosis so that delays in treatment can be avoided. HAEC treatment includes bowel rest, intravenous fluid hydration, correction of electrolyte imbalance, rectal irrigations, and broad-spectrum antibiotics. (41) If the infant does not improve despite this treatment, urgent ostomy creation for fecal diversion should be considered. (3)

If anal dilations and/or rectal irrigations are effective at decompressing the colon, the child's caregivers can be taught to perform these techniques and the infant can be discharged from the hospital. The optimal timing of operative intervention for short-segment HSCR is debated and varies depending on the surgeon's preference. In general, many pediatric surgeons perform a pull-through procedure within the first 6 months of life.

SURGICAL MANAGEMENT

The principle underlying operative treatment of HSCR is to remove the aganglionic segment and anastomose the proximal, normally ganglionated bowel to the anal canal, being careful not to injure the anal sphincter complex or the pelvic innervation. The determination of where normal enteric ganglia are present requires intraoperative biopsies of the bowel with frozen section evaluation by an experienced pathologist. Short-segment aganglionosis is commonly treated with a single-stage transanal procedure using either a Swenson or a Soave procedure. (42)(43) In the Soave pull-through procedure, the rectal muscle is left in place and the more proximal ganglionic bowel is pulled down through this muscular cuff and anastomosed to the anus. This is done to avoid dissection around the rectum, where the pelvic innervation is located. In contrast, the Swenson procedure includes a full-thickness dissection of the rectum. Another commonly used procedure is the Duhamel operation, which involves a retrorectal dissection and preservation of the aganglionic rectum. The proximal ganglionated bowel is brought down behind the rectum and a side-to-side anastomosis is performed. This creates a neorectum that can function as a reservoir for stool and which is composed of normally innervated colon posteriorly and aganglionic rectum anteriorly. Although half of the neorectum is aganglionic, it is capable of water absorption and thus can reduce the volume and frequency of stool. When comparing postoperative complications (anastomotic leak, stricture, or enterocolitis) and postoperative anorectal function (constipation or fecal incontinence), there does not appear to be any significant differences among the Soave, Swenson, and Duhamel procedures. (44)

Long-segment HSCR is typically treated with a staged approach. In the first operation, a leveling ostomy is performed, as described earlier. The second operation, performed at 1 to 3 years of age depending on surgeon preference, involves removing the aganglionic bowel, taking down the ostomy, and anastomosing it to the anus. The anastomosis of the ganglionated proximal bowel can be performed as a straight ileoanal anastomosis using a Swenson or Soave technique. For total colonic aganglionosis, however, the authors prefer the Duhamel procedure, because it brings ganglionated ileum to the anus and creates a neorectum that can function as a reservoir and is capable of water absorption, thus decreasing the morbidity often associated with frequent passing of stools.

The operations described here rely on the expertise of a pathologist experienced in the evaluation of enteric ganglia to determine where normal ganglia are present. If the pathologist or surgeon is uncertain about the level of aganglionosis, the safest option is to perform multiple biopsies, leave an ileostomy, and await a definitive pathologic diagnosis before proceeding with a pull-through procedure. Importantly, even when the pathologist identifies the level at which ganglion cells are present, it is recommended that the pediatric surgeon remove an additional 5 cm of bowel proximal to that point. (45) This will decrease the risk of creating a "transition zone" pull-through, which occurs when a relatively hypoganglionic segment of bowel located between aganglionic and normoganglionic bowel is used for the pull-through, thus resulting in postoperative obstructive symptoms often requiring reoperation.

POSTOPERATIVE CLINICAL MANAGEMENT

For patients with HSCR, postoperative management focuses mainly on controlling pain, monitoring for stool output, and resuming enteral feedings once bowel function returns. Starting 1 week postoperatively, the surgeon will often initiate daily anal dilations to prevent the development of an anastomotic stricture. (3) Some surgeons advocate routine postoperative rectal irrigations starting 1 to 2 weeks postoperatively and continuing for 3 months because this has been shown to reduce the risk of postoperative HAEC. (46) Finally, care of the perianal skin is a high priority because the skin breakdown from liquid, high-frequency stool can be a major challenge for children and their parents. Barrier creams should be started immediately after pull-through surgery and before the first postoperative bowel movement to help prevent perianal skin breakdown secondary to frequent stooling.

OUTCOMES/PROGNOSIS

Clinical outcomes after surgical management of HSCR can be divided into early postoperative complications, long-term bowel function, and quality of life. Early complications are the same as those commonly encountered after any colorectal surgery and include bleeding, infection, anastomotic dehiscence, stoma complications, and anal mucosal prolapse. Long-term complications are dominated by obstructive symptoms, fecal incontinence, and HAEC, and represent the major causes of morbidity in these patients. (47) These are discussed in detail here.

Obstructive symptoms are characterized by difficulty evacuating stool and abdominal distention. The incidence of obstructive symptoms is about 5% to 33% and can persist into adolescence and adulthood. (48) The causes can be categorized into 5 categories, with treatments tailored to each (49)(50):

1. Mechanical obstruction. This can be caused by anastomotic strictures at the coloanal anastomosis, twisting of the pull-through bowel, or failure to divide the muscular cuff in a Soave procedure. Strictures can sometimes be treated with dilation, but each of these complications may necessitate revision surgery.
2. Internal anal sphincter dysfunction. As discussed before, absence of the RAIR in HSCR leaves a nonrelaxing sphincter that can make evacuation of stool difficult. This is often treated with injection of botulinum toxin to relax the internal anal sphincter and lower its resting pressure.
3. Transition zone pull-through. If aganglionic, hypoganglionic, or otherwise abnormally innervated bowel is retained, its motility may be impaired. Rectal biopsy is required to make this diagnosis, and a pull-through is then repeated.

4. Colonic dysmotility. Even when ganglion cells appear to be normal, colonic motility may not be normal, and the pathophysiology of this remains unknown. Causes may include defective enteric neurons, neuronal subtype imbalance, (51)(52) or abnormal interstitial cells of Cajal. (53) Repeat surgery, diverting ostomy, or aggressive bowel management should be considered.
5. Functional constipation. Children with a history of anal surgery, repeated anorectal manipulation, or painful defecation can develop an aversion to passing stools and this can lead to withholding behavior and severe constipation. Treatments include bowel management and behavioral intervention.

Fecal soiling or incontinence is relatively common in patients with HSCR, with reported rates of 36% to 48%. Only about half of all adolescents and adults who had surgery for HSCR during childhood achieve bowel function scores comparable to those of control subjects. (48) Some cases of soiling may be due to pseudoincontinence, which occurs because of overflow of stool around an impacted fecal mass; this needs to be treated as severe constipation. However, true incontinence also occurs. One cause for this may be the removal of the rectum, which is part of the Soave or Swenson procedure. The rectum has an important function as a reservoir for stool. It also stops the high-amplitude propagating contractions (HAPCs) that propel stool along the colon. After proctectomy, the fecal reservoir is gone and the HAPCs can now progress down to the anal canal, significantly contributing to soiling risk. In addition, colonic resection is known to be associated with an increase in the frequency and amplitude of HAPCs, exacerbating the problem. Finally, iatrogenic injury to the anal sphincters or pelvic innervation can also contribute. Management options include antimotility agents, amitriptyline to reduce HAPC frequency and amplitude, (54) a constipating diet, or antegrade enemas to empty the colon (55) and thereby prevent soiling.

HAEC remains a risk even after a successful pull-through operation. The reported incidence of HAEC varies widely in the literature because of the lack of a consensus definition and significant variability in diagnosis by clinicians. HAEC is estimated to occur in 6% to 60% of patients before definitive pull-through surgery and in 2% to 42% after surgery. (38)(39)(56) Those at increased risk for developing HAEC include children with a family history of HSCR, trisomy 21, long-segment aganglionosis, preoperative HAEC, and postoperative obstruction from any cause. (38)(39)(40)(56)(57) The etiology of HAEC remains a topic of much debate and investigation. Evidence suggests that it is multifactorial with a complex combination of changes in the innate immune system, epithelial barrier function of the gut, and/or intestinal microbiome composition. (38)(57)(58) Management of mild HAEC includes outpatient treatment with oral metronidazole and rectal irrigation. More severe cases require inpatient admission for broad-spectrum antibiotics, intravenous fluids, and rectal irrigations. Promisingly, with aggressive treatment strategies, the mortality associated with HAEC has decreased substantially from 3% to 30% to less than 1% over the past several decades. (56)

Quality of life can be affected in patients with HSCR. Compared with healthy children, many children with a diagnosis of HSCR exhibit a reduction in psychosocial quality of life. Worsening psychosocial function is associated with increasing age and with the presence of fecal incontinence or dysfunctional elimination. (59) Children with problems of fecal control often lose self-confidence, shy away from social relationships, and dislike going to school. (44) Adults treated for HSCR as children also report lower emotional quality-of-life scores and limitations in their personal and sexual relationships secondary to the presence of incontinence. (60) This growing awareness of the long-term complications of the disease and the impact on quality of life highlights the need to improve our management of HSCR with the goal of decreasing the morbidity associated with this disease and its treatment.

FUTURE DEVELOPMENTS IN THE MANAGEMENT OF HSCR

One area of active and promising research is the development of possible nonoperative approaches for the management of HSCR. This includes the development of neuronal stem cell transplantation for HSCR and other neurointestinal diseases. (52) By identifying and isolating neuronal progenitor cells from the human postnatal intestine, (61) it may be possible to transplant these cells to areas of intestine that are missing or have abnormal neurons. This was recently successfully completed in a mouse model in which researchers isolated enteric neuronal progenitors from the intestine or differentiated them from pluripotent stem cells and then transplanted these progenitors into mouse models of HSCR. (62)(63) At this time, improvement in gut function has yet to be convincingly demonstrated, but research continues in this field and human pilot studies are on the horizon.

Another area in need of improvement to decrease the morbidity associated with HSCR is the approach to HAEC. The first clinical challenge related to HAEC is the lack of clinical criteria to make the diagnosis. (39) As a result, the incidence and cause of HAEC remain unknown despite being first recognized nearly 60 years ago. Given that HAEC remains the most common cause of mortality in children with HSCR, (38)(39)(40) understanding its etiology remains a priority. Recent literature has examined longitudinal changes in the microbiome composition in children with HSCR during and between episodes of HAEC (64)(65) to attempt to identify a group of bacteria that may be responsible for the development of HAEC. However, at this time there is no convincing evidence that shows a definitive causal relationship between any specific group of bacteria and microbiome dysbiosis leading to HAEC.

Finally, several recent publications have discussed the need to directly address the decreased quality of life experienced by patients with HSCR. One study suggests that the involvement of psychologists or mental health professionals in the long-term management of HSCR in children is critical to improve social and emotional quality-of-life outcomes. (59) Another recent publication focused on the need to address transitions from childhood/adolescent care to adult care. (66) This study identified a high prevalence of ongoing symptoms related to abnormal bowel function and a resultant low quality of life. Despite this, very few, if any, patients have had conversations regarding how they will make a transition into adult care. Thus, there are often lapses in care that can further decrease a patient's quality of life. (66) To best serve this patient population, smooth transitions of care from childhood into adulthood are imperative to make certain that their medical needs are adequately met by the appropriate providers.

CONCLUSIONS

HSCR remains the most common congenital neurointestinal disease affecting neonates. Significant advances have been made over the past several decades in our understanding of the disease, its diagnosis, and its management. However, long-term outcomes remain suboptimal, providing important opportunities to improve treatment of these patients. Some of the key points reviewed in this article are as follows:

1. Diagnosis of HSCR in neonates begins with a high clinical suspicion and includes a contrast enema and rectal biopsy.
2. Once HSCR is diagnosed, colonic decompression is achieved with anal dilations and/or rectal irrigations to minimize fecal stasis and colonic dilation until surgery is performed.
3. Surgical treatment of HSCR involves removal of the aganglionic segment of bowel and anastomosis of the proximal, normally ganglionated bowel to the anal canal. The early and long-term outcomes of the 3 most common procedures (Soave, Swenson, and Duhamel) are similar.
4. HAEC requires prompt diagnosis and treatment with rectal irrigations, antibiotics, and fluid resuscitation in those with severe enterocolitis.
5. Long-term follow-up of patients with HSCR is essential to improve gastrointestinal function and enhance quality of life.

Note. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Understand the differential diagnosis of delayed passage of meconium.
- Know the pathological, clinical, and diagnostic features of Hirschsprung disease, including other associated clinical conditions.
- Know the management and complications of treatment of Hirschsprung disease.

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1. Hirschsprung disease is a common cause of neonatal bowel obstruction, with an incidence of 1 in 5,000 live births. The incidence of Hirschsprung disease has been shown to vary among different ethnic groups. Which of the following groups has the highest incidence of Hirschsprung disease?
   - A. Hispanics.
   - B. Whites.
   - C. Blacks.
   - D. Asians.
   - E. Native Americans.

2. Hirschsprung disease is a disease of the enteric nervous system. It is characterized by failure of neural crest cells to complete their craniocaudal migration, leaving a portion of the colon aganglionic and functionally obstructed. Which of the following statements regarding the pathophysiology of Hirschsprung disease is correct?
   - A. Neural crest cells complete their craniocaudal migration by week 12 of gestation.
   - B. Most cases of Hirschsprung disease are sporadic, with only about 10% of cases being familial.
   - C. Familial cases are more often associated with short-segment Hirschsprung disease.
   - D. Syndromic Hirschsprung is uncommon, accounting for about 15% of cases.
   - E. Coding and noncoding mutations in the receptor tyrosine kinase (*RET*) gene are the most common mutations associated with Hirschsprung disease.

3. The majority (94%) of full-term infants will pass meconium 24 hours after birth whereas 99.8% do so within 48 hours of birth. Infants with Hirschsprung disease typically have delayed passage of meconium, with only 6% passing meconium by 24 hours after birth. What is the proportion of infants with Hirschsprung disease that will pass meconium by 48 hours?
   - A. Less than 10%.
   - B. 15% to 25%.
   - C. 40% to 50%.
   - D. 60% to 70%.
   - E. Greater than 80%.

4. A term neonate presents with abdominal distention and failure to pass meconium at 48 hours. You suspect Hirschsprung disease and order a water-soluble contrast enema. Which of the following statements regarding the characteristics of Hirschsprung disease on contrast enema is correct?
   - A. A rectosigmoid ratio greater than 1 is suggestive of Hirschsprung disease.
   - B. A transition zone is observed in 85% of patients with Hirschsprung disease.
   - C. The presence of a transition zone reliably predicts the length of the aganglionic segment.
   - D. A sawtooth or speculated appearance of the rectal mucosa can be observed in 75% of patients with Hirschsprung disease.
   - E. The sensitivity of the contrast enema in the case of long-segment Hirschsprung is less than 50%.

5. Despite surgical correction, patients with Hirschsprung disease are at risk for long-term complications including obstructive symptoms, fecal incontinence, and Hirschsprung-associated enterocolitis. Which of the following statements regarding long-term complications of Hirschsprung disease is correct?

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A. About 70% of adolescents and adults who had surgery for Hirschsprung disease achieve bowel function scores comparable to those of control subjects.
B. Increased amplitude and frequency of high-amplitude propagating contractions after a colonic resection contribute to fecal soiling and incontinence in patients with a history of Hirschsprung disease.
C. Obstructive symptoms, such as difficulty evacuating stool and abdominal distention, affect about 50% of adult patients with a history of Hirschsprung disease.
D. Hirschsprung-associated enterocolitis is more common after surgical repair than it is before pull-through surgery.
E. Hirschsprung-associated enterocolitis is less common in patients with a family history of Hirschsprung disease.

Radiologic Approach to the Diagnosis of Bowel Emergencies in Neonates

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Education Gaps

1. Several neonatal bowel disorders have similar clinical presentations, and require prompt diagnosis and treatment to minimize morbidity and mortality; therefore, there is a need for appropriate imaging strategies to optimize outcomes.
2. While conventional radiography and fluoroscopic studies are the mainstays in the diagnosis of many neonatal bowel disorders, the role of ultrasonography and magnetic resonance imaging in this clinical setting has expanded.

Abstract

Neonatal bowel disorders represent a diverse set of congenital and acquired conditions spanning the alimentary tract. Clinical presentation is variable and reflects both the site of gastrointestinal involvement as well as the underlying pathology. Several of the neonatal bowel disorders represent true surgical emergencies and require prompt diagnosis for optimal outcomes. Radiologic studies, which may consist of radiography, upper gastrointestinal series, barium enema, and/or ultrasonography, provide essential data to achieve the correct diagnosis.

Objectives

After completing this article, readers should be able to:

1. Identify salient clinical and radiologic features of the most common neonatal bowel disorders.
2. Describe an appropriate imaging algorithm for symptoms of common neonatal bowel disorders.

AUTHOR DISCLOSURE Drs Ngo and Phillips have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

EA	esophageal atresia
HD	Hirschsprung disease
HPS	hypertrophic pyloric stenosis
MRI	magnetic resonance imaging
NEC	necrotizing enterocolitis
TCON	transient colonic obstruction of the newborn
TEF	tracheoesophageal fistula
UGI	upper gastrointestinal

INTRODUCTION

Neonatal bowel disorders are commonly encountered in the setting of the NICU. The most frequent neonatal disorders of the upper gastrointestinal (UGI) tract are esophageal atresia (EA) and tracheoesophageal fistula (TEF), hypertrophic pyloric stenosis (HPS), duodenal atresia, duodenal web and stenosis, and malrotation. The lower intestinal tract pathologies that are most commonly seen include small-bowel atresias, meconium ileus, transient colonic obstruction of the newborn (TCON), Hirschsprung disease (HD), necrotizing enterocolitis (NEC), anorectal malformations, and imperforate anus. We review the typical presenting features of neonatal bowel disorders, with an emphasis on the radiologic diagnosis. Although the focus of this article is postnatal presentation and diagnosis, some conditions such as duodenal atresia, may be diagnosed prenatally using ultrasonography or fetal magnetic resonance imaging (MRI).

IMAGING APPROACH

Conventional radiography, consisting of a frontal supine view of the abdomen, is generally the initial radiographic examination in neonates presenting with possible symptoms of a bowel disorder, such as feeding intolerance, bilious or nonbilious emesis, abdominal distention, or failure to pass meconium. Ideally, external monitoring devices and comfort pads should be eliminated from the area of interest to maintain image quality and minimize radiation dose. (1)(2) For suspected esophageal pathologies, the field of view may be expanded to include the chest. Symptoms of perforation or obstruction warrant a left lateral decubitus or cross-table lateral view to exclude free intraperitoneal air, portal venous gas (note: this can be visualized in any view but sometimes is better seen on left lateral decubitus because the bowel is moved away from the right upper quadrant), and differential air-fluid levels. Of note, distal gas in the rectum is best confirmed with prone positioning. The results of conventional radiography, combined with the clinical picture, guide further management.

Conventional radiography may be diagnostic for certain neonatal bowel disorders, such as duodenal atresia (ie, “double bubble” sign). In addition, the presence of a few dilated bowel loops on conventional radiographs suggests a proximal bowel obstruction, whereas multiple dilated bowel loops are seen with a distal bowel obstruction. In the absence of a definitive diagnosis on initial radiography, a UGI series is performed for suspected proximal obstruction and to investigate the anatomy of the esophagus, stomach, and proximal small bowel. A contrast enema is used to evaluate suspected distal obstruction, as well as to delineate possible abnormalities of the rectum, colon, and distal small bowel. A few neonatal bowel disorders, such as suspected hypertrophic pyloric stenosis (HPS), fall outside this imaging paradigm, which will be further discussed in this article. In addition, the expanding role of cross-sectional imaging, particularly in the form of ultrasonography and MRI, will be highlighted as it pertains to specific neonatal bowel disorders.

NEONATAL BOWEL DISORDERS OF THE UGI TRACT

EA and TEF

EA and TEF may occur in isolation or in association with each other. The estimated incidence of EA is 1 in 2,500 to 3,000 live births. (3) The Gross classification system categorizes the anomalies as follows (4):

- Type A: Isolated EA without TEF
- Type B: EA with an associated proximal TEF
- Type C: EA with an associated distal TEF
- Type D: EA with proximal and distal TEF
- Type E: Isolated TEF

Additional congenital abnormalities of the cardiovascular, musculoskeletal, gastrointestinal, and genitourinary systems are frequently found in this population. (4) "VACTERL" refers to patients with 3 or more congenital abnormalities of the vertebral, anorectal, cardiac, tracheal, esophageal, renal, and limb systems while lacking a specific chromosomal aberration.

Prenatal ultrasonography may suggest EA in cases of polyhydramnios combined with an absent stomach bubble, with a sensitivity of 32%. (5) Patients with undiagnosed EA usually present in the early postnatal period with difficulty feeding, excessive oral secretions, and cyanosis or apneic spells while feeding. (4) The inability to successfully pass a nasogastric tube strongly suggests EA. Abdominal radiographs show absent bowel gas in patients with Gross type A and B, isolated EA (Fig 1), and EA with proximal fistula, respectively. Flexible esophagoscopy or flexible bronchoscopy is the preferred diagnostic test for TEF associated with EA, which typically better delineates patient anatomy compared with contrast studies. (6)(7) The risk of aspiration is a relative contraindication for UGI series in patients with EA. (8) However, UGI series is commonly used after surgical repair to diagnose anastomotic leak and stricture, which occur in 15% to 20% and 30% to 40% of these patients, respectively. (4)

HPS

HPS is a functional gastric outlet obstruction resulting from abnormal thickening and elongation of the pylorus. Current understanding of the condition suggests that both environmental and genetic factors contribute to its development. Commonly recognized risk factors include male sex, primiparity, prematurity between 28 and 36 weeks' gestational age, and postnatal erythromycin exposure. (9) Five genetic loci are associated with HPS. (9) Affected patients are typically between 2 and 12 weeks of age and present with nonbilious, projectile emesis. (9) Earlier diagnosis likely explains the reported decreased frequency of the well-described palpable "olive," consisting of the thickened, elongated pyloric channel, on physical examination. (10)

HPS may be diagnosed with either UGI series or ultrasonography, with the latter now favored because of its high sensitivity and specificity without the use of ionizing radiation. Ultrasonography allows measurement of the pyloric channel thickness and length, with diagnostic thresholds being 3 mm and 15 mm, respectively (Fig 2). (11) Dynamic evaluation reveals minimal if any egress of gastric contents through the pyloric channel. Pylorospasm, a temporary condition that may mimic HPS on imaging, can be excluded by prolonging or repeating the examination. (9)

Duodenal Atresia, Duodenal Web, and Duodenal Stenosis

Duodenal atresia is caused by the failure of gut recanalization during embryology, with a resulting complete obstruction. The incidence of duodenal atresia is approximately 1 in 10,000. Duodenal atresia may be seen in isolation or in the setting of trisomy 21. Prenatal ultrasonography shows polyhydramnios and a sonographic "double bubble" representing a dilated stomach and proximal duodenum. If undiagnosed prenatally, neonates typically present with bilious or nonbilious emesis. On conventional radiographs, a radiographic double bubble finding is diagnostic of duodenal atresia (Fig 3), in which there is pronounced gaseous dilation of both the stomach and duodenal bulb in an otherwise gasless abdomen. In rare instances, distal bowel gas is present when an anomalous biliary duct spans the atretic duodenal segment, (12) in which case, UGI series may be necessary to definitively diagnose duodenal atresia.

Duodenal stenosis and web cause partial obstruction, by a narrowed segment or thin membrane, respectively, because of incomplete recanalization of typically the second segment of the duodenum during embryology. Both entities may be diagnosed with UGI series. With duodenal stenosis, a focal narrowing is seen of the contrast column in the second portion of the duodenum. With duodenal web, a "windsock" deformity can be seen as contrast fills the dilated proximal duodenal segment, and outlines a thin web that bulges into the nondilated distal segment. A similar phenomenon may be seen on ultrasonography if fluid or gas distends the distal duodenum. (13) Of importance, there is a high incidence of malrotation, annular pancreas, and a preduodenal vein with both duodenal stenosis and web.

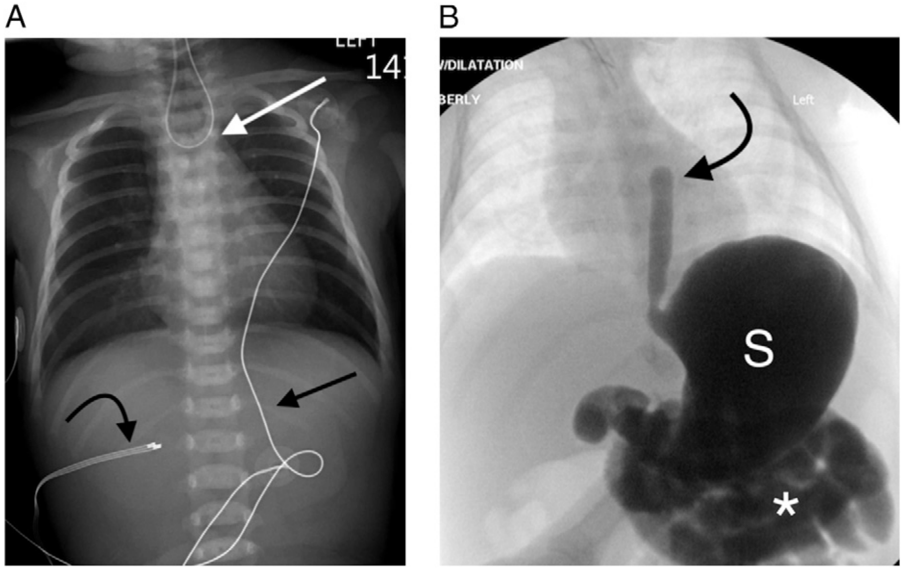

Figure 1. Esophageal atresia. Female neonate on the day of birth with choking seen on feeding and difficulty passing feeding tube. A. Frontal radiograph demonstrates feeding tube looped within the proximal esophageal pouch (white arrow). There is an absence of bowel gas in the visualized upper abdomen. Monitoring devices consisting of a temperature probe (curved black arrow) and a monitoring lead (straight black arrow) are also visualized. B. Frontal fluoroscopic image from the operating room demonstrates radiopaque contrast within the distal, blind-ending esophageal pouch (curved arrow), as well as contrast within the stomach (S) and small bowel (asterisk).

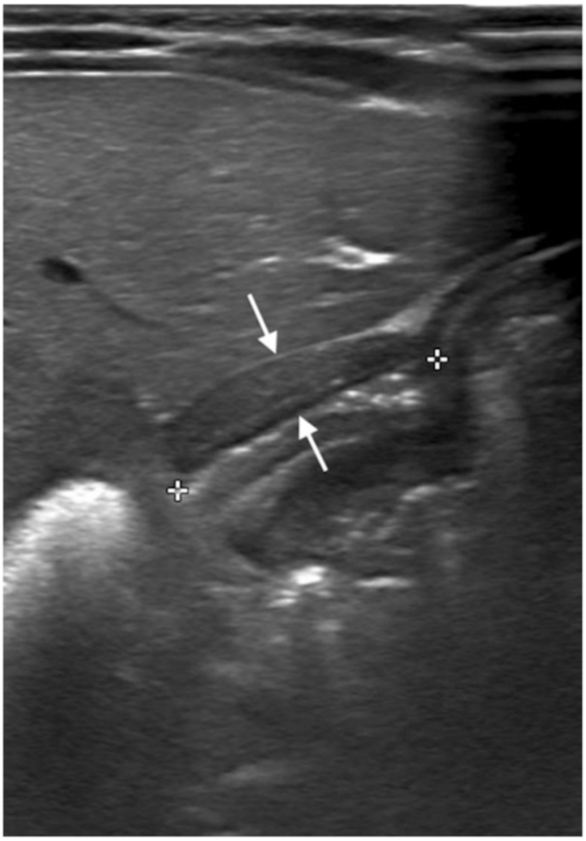

Figure 2. Pyloric stenosis. Two-month-old boy with feeding intolerance. Transverse ultrasound scan shows an elongated, thickened pylorus with length of 24 mm demarcated by the plus (+) sign and single muscular wall thickness of 5.5 mm demarcated by white arrows.

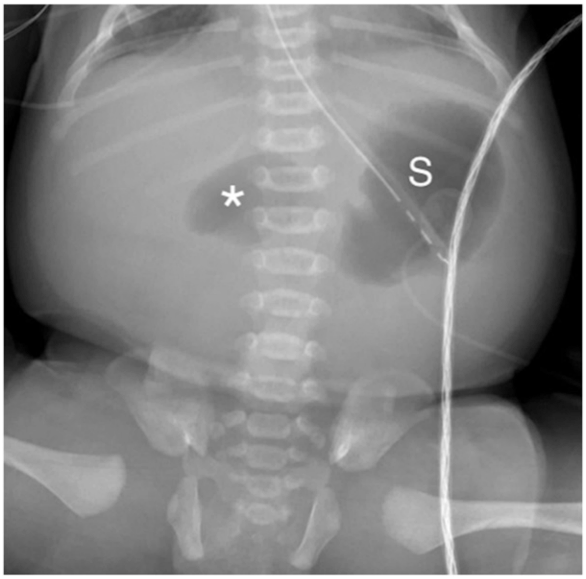

Figure 3. Duodenal atresia. Female neonate on the day of birth with prenatally diagnosed duodenal atresia, trisomy 21, and balanced atrioventricular canal. Frontal radiograph of the abdomen demonstrates a "double bubble" sign with gaseous distention of the stomach (S) and dilated duodenum (asterisk), characteristic of duodenal atresia.

Intestinal Malrotation

Intestinal malrotation arises from the abnormal rotation and fixation of the bowel during embryology, which results in an abnormally narrow mesenteric pedicle that predisposes patients to midgut volvulus and intestinal ischemia. In addition, peritoneal bands that abnormally fix the malpositioned bowel may cause bowel obstruction. The estimated prevalence of malrotation is approximately 1 in 500 live births. (14) Several conditions are highly associated with malrotation, including congenital diaphragmatic hernia, omphalocele, and heterotaxy syndrome. Malrotation may also be seen with duodenal/intestinal atresia or web, biliary atresia, Meckel diverticulum, and HD. (11)(15) The classic presentation of malrotation is bilious emesis with abdominal distention. (16) Patients with midgut volvulus may present with abdominal pain, distention, hematochezia, and hypovolemic/septic shock with peritoneal signs. Preterm infants with volvulus may also present with nonspecific symptoms such as gastric retention and apnea. (17)

Abdominal radiographs may be normal in the setting of malrotation and volvulus. UGI series is the preferred imaging study for the diagnosis of malrotation and volvulus, (14)(18)(19) with sensitivities of 93% to 100% and 56% to 79%, respectively. (20)(21)(22)(23) In malrotation, the duodenal-jejunal junction, or ligament of Trietz, is abnormally low and either near midline or to the right of midline (Fig 4). This is in contrast to the normal position of the duodenal-jejunal junction, at or to the left of the left pedicles of the vertebral column, and at the level of the duodenal bulb. Of note, nonrotation is considered an incidental finding in 2 of 100 UGI series, in which bowel rotation does not occur during embryology, resulting in small bowel occupying the right abdomen and large bowel within the left abdomen. (24) In nonrotation, the risk of volvulus is considered low because of a broad mesenteric root. A false-positive rate of up to 15% of UGI series for malrotation is seen with anatomic variants such as a redundant duodenum and duodenum inversum. (19) In addition, the position of the duodenal-jejunal junction may be displaced or distorted by such factors as ligamentous laxity in patients younger than 4 years, feeding tubes, and mass effect from organomegaly or tumors. (14)(19)(25) If UGI series results are equivocal, small-bowel follow-through or a contrast enema may be considered to document cecal position, and thus interpolate the length of the mesenteric root.

Ultrasonographic findings such as an inverted relationship of the superior mesenteric artery and vein may raise the possibility of malrotation, though this finding may also be seen in 3% of patients with normal rotation. (26) In

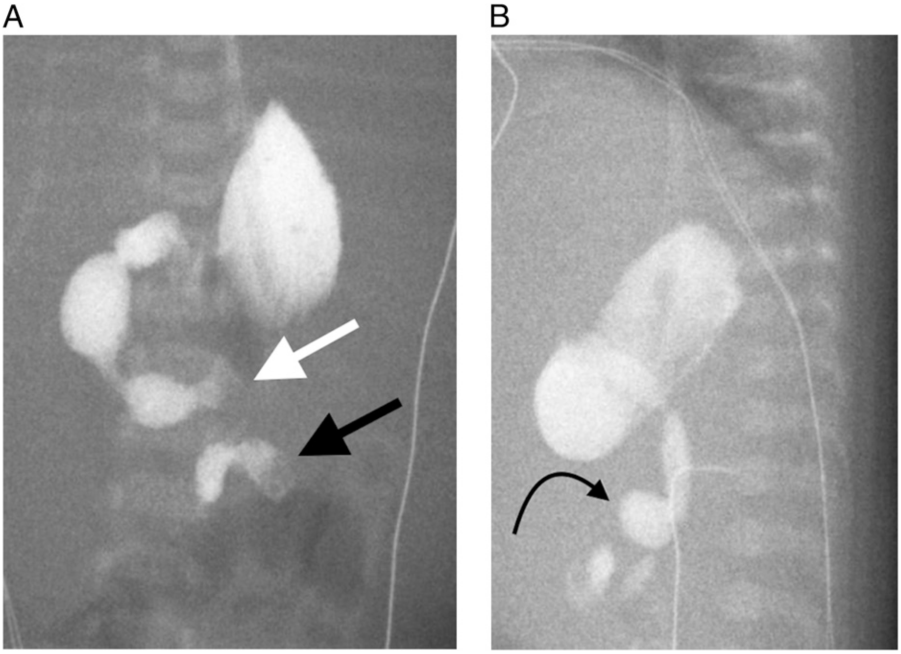

Figure 4. Malrotation with volvulus. One-day-old girl with prenatally diagnosed dilated bowel loops and bilious gastric secretions at birth. A. Frontal image from an upper gastrointestinal (UGI) series demonstrates an abnormally low position of the ligament of Treitz (white arrow) and a twisted configuration of the proximal jejunum (black arrow) consistent with malrotation with volvulus. B. Lateral image from the UGI series demonstrates an abnormal anterior course of the third portion of the duodenum (curved black arrow).

addition, ultrasonography has been used to document an abnormal, intraperitoneal position of the third portion of the duodenum lacking the normal configuration of the duodenal sweep; however, acceptance of this technique remains controversial. (27) In midgut volvulus, ultrasonography can demonstrate the twisted mesenteric vessels that give rise to the "whirlpool sign." The use of MRI in diagnosing malrotation in asymptomatic individuals was studied by Fay et al, who reported a sensitivity of 75% and specificity of 76% for abnormal rotation. (28)

NEONATAL BOWEL DISORDERS OF THE LOWER GASTROINTESTINAL TRACT

Small-Bowel Atresia

Small-bowel atresia is thought to result from an ischemic insult, and can occur anywhere along the length of the small bowel. The incidence of jejenoileal atresia is 1 in 3,000 to 5,000 live births. (29) It typically presents early in life with bilious emesis, abdominal distention, and, in the case of distal obstructions, failure to pass meconium. On conventional radiography, faint peritoneal calcifications are sometimes visible in cases of in utero perforation. Proximal atresia of the jejunum can result in a characteristic “triple bubble” pattern, with 3 dilated hollow visci corresponding to the stomach, duodenum, and a proximal jejunal segment (Fig 5). If a triple bubble pattern is present, then further diagnostic studies may not be required.

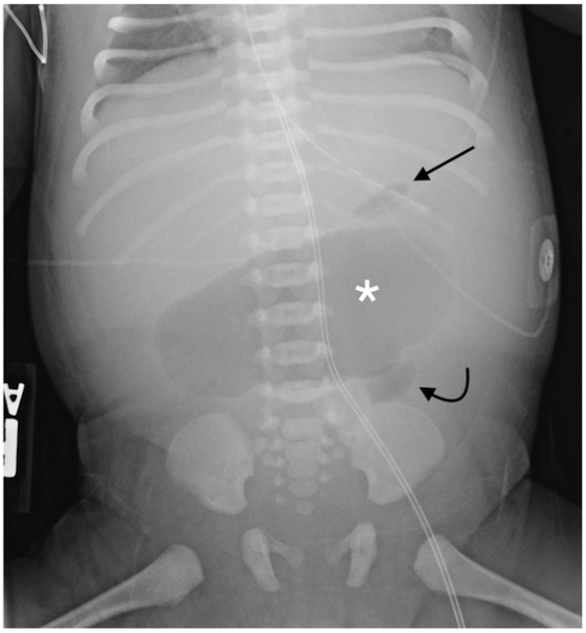

Figure 5. One-day-old boy with proximal jejunal atresia. Frontal radiograph shows a "triple bubble" pattern, with the stomach decompressed by the enteric tube (black straight arrow), severe dilation of the duodenum (asterisk), and a small amount of gas in the jejunum (curved black arrow).

However, if radiographs reveal multiple dilated bowel loops, a contrast enema is the next diagnostic imaging test.

In distal ileal atresia, contrast enema typically reveals a microcolon, in which the entire colon is diffusely narrow in caliber, reflecting a relatively "unused" colon related to discontinuity from nearly the entire small bowel. In jejunal or more proximal ileal atresia, the colon may appear normal on contrast enema because there is a longer segment of small bowel in continuity with the colon, creating a normal "used" appearance.

Meconium Ileus

Meconium ileus is a neonatal small-bowel obstruction that results from thick tenacious meconium that fills the distal small bowel. Up to 90% of full-term neonates with meconium ileus also have cystic fibrosis, which alters the chloride ion exchange, causing dehydration of the intraluminal bowel contents and resultant thickened meconium. (30) The incidence of cystic fibrosis is 1 in 3,500 live births of white infants. (31)

On conventional abdominal radiography, uncomplicated cases demonstrate diffuse small-bowel dilation, sometimes with a frothy appearance of distal small-bowel loops in the right lower quadrant related to inspissated meconium. Complicated cases of meconium ileus, defined as associated segmental volvulus, atresia, necrosis, or perforation, may have a more variable appearance. (32) In addition, complicated cases may also present with peritoneal calcifications secondary to perforation. Meconium pseudocyst, related to a walled-off perforation, should be suspected if conventional radiography demonstrates a paucity of gas within a quadrant or a rounded rim of calcification (Fig 6A). Ultrasonography can characterize the fluid components of pseudocysts, for example, by detecting internal septations (Fig 6B).

As with other distal small-bowel obstructions, fluoroscopic evaluation of meconium ileus characteristically reveals a microcolon (Fig 6C). Contrast material refluxed into the distal small bowel may outline small filling defects consisting of tenacious meconium. Water-soluble contrast is not only diagnostic but also therapeutic by facilitating passage of the inspissated meconium, thus potentially relieving the obstruction and obviating surgery. Success rates are variable, ranging from 5% to 83%. (32) Of note, diatrizoate is no longer used for contrast enemas because of its much higher osmolality compared with more recently developed contrast agents.

Hirschsprung Disease

HD causes a functional obstruction of the colon due to a disorder of the enteric nervous system characterized by absence of ganglion cells of the rectum and variable lengths of the colonic submucosal and myenteric plexus. The affected segments fail to relax, creating a relative state of spasm, and thus leading to functional obstruction. Although HD may occur in girls, a male predilection as high as 5:1 has been reported. (33) The overall incidence of HD is 1 in 5,000 live births. (34) Neonates with HD typically present with failure to pass meconium.

Conventional radiography typically demonstrates diffuse dilation of multiple bowel loops signifying a distal obstruction. Peritoneal calcifications are absent because perforation is not typically associated with HD. Although definitive diagnosis is made based on suction biopsy of the rectum, contrast enema is often performed. Contrast enema often reveals a narrow-caliber rectum relative to the remainder of the colon, with a rectosigmoid diameter ratio of less than 1 (Fig 7). Dynamic fluoroscopic imaging can show a sawtooth pattern of the rectal contour from the unopposed contractions of the rectum. Variable lengths of

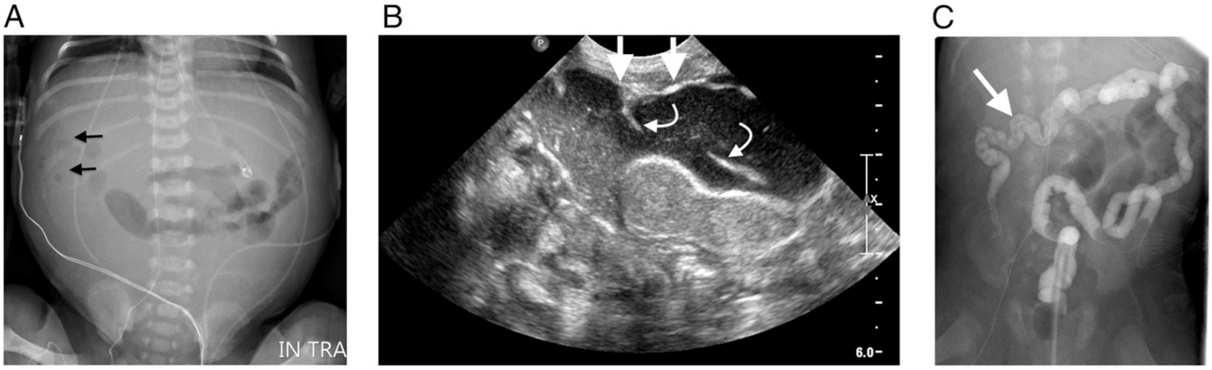

Figure 6. One-day-old boy with meconium ileus and pseudocyst formation. A. Frontal conventional radiograph of the abdomen shows peripheral peritoneal coarse calcifications in the right upper quadrant (arrows). B. Transverse ultrasound image of the right abdomen shows a thick-walled fluid collection (short white arrows) with mild septations (curved white arrows) and heterogeneous contents. C. Frontal view from a contrast enema shows a characteristic microcolon with small filling defects (arrow) in the proximal colon secondary to thickened meconium.

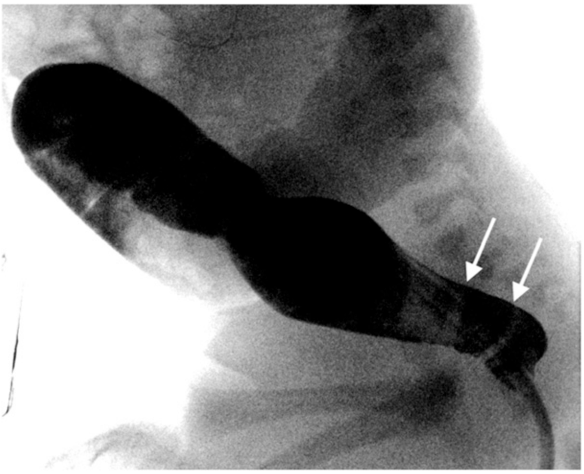

Figure 7. Hirschsprung disease in a neonate. Lateral image from a fluoroscopic contrast enema shows an abnormally narrowed rectum (arrows), with an abnormal rectosigmoid diameter ratio measuring less than 1, suggestive of Hirschsprung disease.

involved contiguous upstream colon may be present, also with a relatively narrow caliber. Often there is an abrupt transition zone between proximally dilated colon and the affected, narrower-caliber distal colon, though the transition zone may not correlate with the pathologic site of aganglionosis at surgery. (35) A rare form of total colonic HD may have a characteristic "comma-shaped" or "question mark" appearance of the colon. (36)

Transient Colonic Obstruction of the Newborn

TCON is also called functional immaturity of the colon, small left colon syndrome, and meconium plug syndrome. The last term has fallen out of favor because of confusion arising from the similarity in name with another cause of distal bowel obstruction, meconium ileus (discussed previously). Although meconium material is present in the colon in TCON, it is not the underlying cause of obstruction. TCON is thought to arise from immaturity of the ganglion cells or hormone receptors in the colon. There is a higher incidence of affected neonates in children of both diabetic pregnant women and pregnant women treated for preeclampsia with magnesium sulfate. (37) Overall incidence is approximately 1 in 1,000 births. (38)

Similar to other distal bowel obstructive processes, conventional radiographs show dilation of multiple bowel loops. As with HD, peritoneal calcifications are not seen because perforation does not occur. Contrast enema reveals a relatively narrow caliber of the left colon, rather than a diffuse microcolon. Furthermore, in distinction from HD, the rectosigmoid diameter ratio is normal, measuring greater than 1 (Fig 8).

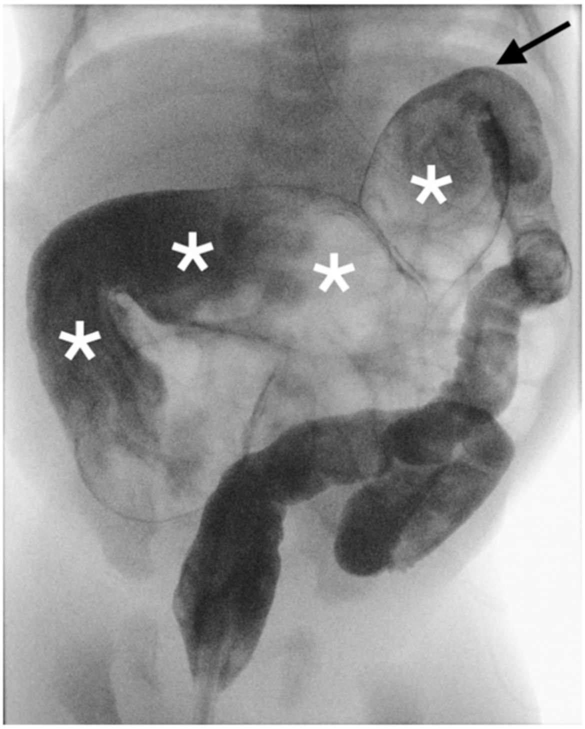

Figure 8. One-week-old girl with transient colonic obstruction of the newborn. Frontal image from a fluoroscopic contrast enema shows a small-caliber left colon, with a transition point at the splenic flexure (black arrow), and upstream dilation of the proximal colon (asterisks). Note that the rectosigmoid diameter ratio is normal (measuring >1), differentiating this entity from variable length Hirschsprung disease.

Necrotizing Enterocolitis

Although NEC is not technically an obstructive entity, it can present clinically with abdominal distention and radiographically with diffuse bowel dilation. NEC remains the most common cause of a neonatal bowel emergency in the NICU setting. (39) Pathogenesis is unknown, and likely multifactorial. NEC is primarily a disease of the premature neonatal population, especially those with birthweights less than 1,500 g (40)(41)(42); however, term infants, particularly those with underlying medical conditions, may also be affected.

Conventional radiography is typically used for initial imaging assessment, as well as to monitor disease progression and guide management. A "NEC watch" consists of a conventional abdominal radiography series every 4 to 12 hours. (43) The radiographic appearance of NEC is variable, and depends on the timing and manifestation of the disease. Early in the disease, diffuse bowel dilation may be the only radiographic sign. As the disease progresses, pneumatosis (which is pathognomonic), sentinel loop dilation, portal venous gas, and even pneumoperitoneum can be present. Although pneumoperitoneum is somewhat insensitive because it is present in less than half of the neonates with

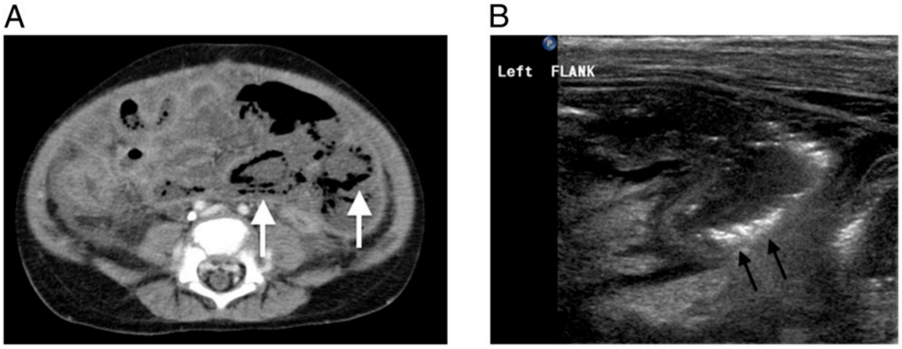

Figure 9. Ten-day-old premature boy with necrotizing enterocolitis. A. Axial computed tomographic image of the abdomen demonstrates gas within the wall of multiple bowel loops consistent with pneumatosis (arrows). B. Ultrasound image of the same patient shows echogenic gas in the dependent portion of the bowel wall, consistent with pneumatosis (arrows).

necrosis and perforation, it remains an absolute indication for urgent surgery. (42)(44)(45)(46)

Diagnosis and monitoring of NEC are increasingly being done with ultrasonography. This is a relatively new approach and as with other ultrasonographic studies, its efficacy is user and experience dependent. The advantages are avoidance of ionizing radiation exposure, and real-time evaluation of bowel peristalsis, mural thickness, and relative vascularization. In addition, pneumatosis and portal venous gas can be detected on ultrasonography with a similar sensitivity as radiography (Figs 9 and 10). (42)(47) In fact, a thin devascularized wall of an aperistaltic bowel segment with associated free complex fluid has been shown to be predictive of adverse outcomes. (47)(48) Further studies are needed on the use of ultrasonography in the diagnosis and monitoring of NEC.

Colonic Atresia and Imperforate Anus

Colonic atresia comprises 3 predominant forms of congenital interruption of the colon, including type 1, a colonic membrane; type 2, discontinuity of the colon with a fibrous band and an intact mesentery; and type 3, a discontinuous colon with a mesenteric defect. (49) Although 3 subtypes have been described, colonic atresia is rare, with an incidence of 1 in 66,000 live births. (50) On conventional abdominal radiographs, the 3 types of colonic atresia are indistinguishable, presenting as diffuse bowel dilation. On contrast enema, the opacified distal colonic caliber is narrow to the level of the atresia, though the rectosigmoid diameter ratio will remain normal, measuring greater than 1. Types 2 and 3 will show an abrupt cutoff at the site of atresia, while type 1 can have a characteristic windsock appearance at the level of the membrane. (51)

Imperforate anus is ordinarily apparent on physical examination immediately after birth. Prenatal ultrasonography can also establish the diagnosis because of failure to visualize a normal anus. Alternatively, upstream fluid dilation of bowel in the setting of polyhydramnios may suggest the diagnosis on prenatal ultrasonography. Most cases are sporadic, but associations with VACTERL

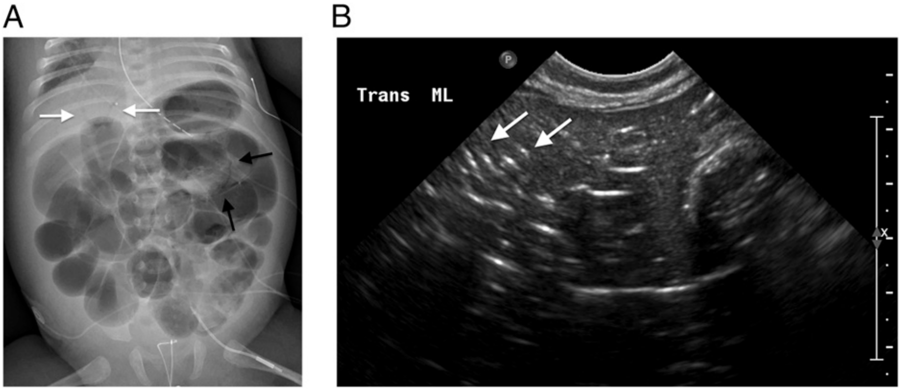

Figure 10. Two-week-old boy with necrotizing enterocolitis. A. Frontal conventional radiograph of the abdomen demonstrates diffuse bowel dilation, as can be seen in distal bowel obstruction. However, careful evaluation of the radiograph also demonstrates portal venous gas in the right upper quadrant (white arrows) and pneumatosis in the left upper quadrant (black arrows). B. Transverse ultrasonographic image of the liver shows echogenic foci throughout the liver consistent with the portal venous gas (arrows).

syndrome and trisomies 18 and 21 have been found. Imperforate anus will demonstrate diffuse dilation of bowel similar to other etiologies of distal obstruction on conventional radiography. In some cases, the bony abnormalities associated with VACTERL syndrome can also be detected. While radiologic evaluation is unnecessary for initial diagnosis, fluoroscopic examination is often performed before definitive corrective surgery.

CONCLUSIONS

Neonatal bowel disorders can present a diagnostic dilemma because of the similarity in presenting signs and symptoms of the various entities. Familiarity with imaging choices, indications, and patterns of disease facilitates prompt diagnosis to minimize morbidity and mortality in this vulnerable population. To summarize:

- Because there are often common presenting features of the various neonatal bowel disorders, as well as the potential need for urgent or emergent intervention, imaging is necessary for accurate, prompt diagnosis.
- By practice guidelines, conventional abdominal radiography is the mainstay of initial evaluation and helps to determine the need for subsequent fluoroscopic studies. If bowel dilation is limited to a proximal distribution, then a UGI series should be considered. However, if the bowel is diffusely dilated, then consider a contrast enema.
- A critically appraised review by Carroll et al of the comparative effectiveness of imaging modalities for the diagnosis of intestinal obstruction in neonates and infants showed a sensitivity of 96% for the fluoroscopic diagnosis of malrotation and a sensitivity of 79% for volvulus. (52) The sensitivity and specificity of contrast enema reported for the diagnosis of HD were 70% and 83%, respectively. (52) Because of a relative paucity of literature, no sensitivities or specificities were reportable for the diagnosis of duodenal atresia or stenosis, jejunal or ileal atresia, transient obstruction of the left colon, or meconium ileus. (52)
- Ultrasonography is the study of choice for HPS, with a sensitivity of 98% and specificity of 100%, (53) and has an increasing role in the evaluation of several other conditions such as meconium pseudocyst and NEC.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the differential diagnosis of bilious and nonbilious vomiting and abdominal distention in the neonate.
- Understand the differential diagnosis of delayed passage of meconium.
- Know the various types and diagnostic features of tracheoesophageal fistulae and esophageal atresias.
- Know the pathogenesis and clinical manifestations of infants with malrotation and/or volvulus of the small intestines.
- Know the approach to diagnosis and management of infants with malrotation and/or volvulus of the small intestine.
- Know the pathophysiology, clinical manifestations, diagnostic features, and management of the meconium plug syndrome.
- Know the pathological, clinical, and diagnostic features of Hirschsprung disease, including other associated clinical conditions.
- Know the management and complications of treatment of Hirschsprung disease.

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1. A term male neonate presents with difficulty feeding, excessive oral secretions, and has an apneic, cyanotic episode. There is inability to pass a nasogastric tube and tracheoesophageal fistula is suspected. In patients with Gross type A and B esophageal atresia, which of the following would be the most appropriate diagnostic imaging strategy and/or finding?
   - A. Double bubble sign on abdominal radiograph.
   - B. Absent bowel gas on abdominal radiograph.
   - C. Screening or confirmatory diagnosis by performing upper gastrointestinal (UGI) contrast study.
   - D. Contraindication for esophagoscopy or bronchoscopy due to concern for unintended perforation.
   - E. Multiple dilated bowel loops on abdominal radiograph.
2. A male infant born at 34 weeks' gestational age presents at 6 weeks of age with bilious, projectile emesis. Abdominal ultrasonography is performed. Which of the following statements regarding risk factors and diagnosis of pyloric stenosis is correct?
   - A. Male sex and prematurity are typically protective factors.
   - B. Genetic risk for pyloric stenosis has yet to be found.
   - C. UGI contrast study is the preferred mode of diagnosis.
   - D. Pylorospasm, observed either on contrast study or ultrasonography, is a pathognomonic sign for the diagnosis of pyloric stenosis.
   - E. Ultrasound measurements of 3-mm pyloric channel thickness and 15-mm channel length are the threshold for diagnosis of pyloric stenosis.
3. A term male infant presents with bilious emesis and abdominal distention at 3 days of age. Soon after admission to the NICU for evaluation, the patient progresses to have bloody stool. However, the patient does not appear to be in pain and has normal blood pressure. There is concern for intestinal malrotation. A UGI contrast study is performed. Which of the following statements concerning this test is correct in this scenario?
   - A. In malrotation, the duodenal-jejunal junction, or ligament of Trietz, is abnormally low and either near midline or to the right of midline.
   - B. In cases of malrotation, UGI study is not particularly more sensitive than abdominal radiography alone, which can diagnose up to 80% of cases.
   - C. Nonrotation, when the small bowel occupies the right abdomen and the large bowel occupies the left abdomen, is seen in ∼10% of newborns.
   - D. An advantage of this test is that the false-positive rate for malrotation is less than 1%.
   - E. In general, UGI series should not be performed when malrotation is suspected because of the risk of perforation.
4. A male infant born at 36 weeks' gestational age is now 3 days old and has not passed meconium. There has also been feeding intolerance, emesis, and mild abdominal distention. Which of the following would increase the suspicion for Hirschsprung disease?
   - A. Abdominal radiograph showing paucity of gas throughout.
   - B. Contrast enema showing narrow-caliber rectum relative to remainder of colon.
   - C. Multiple areas of peritoneal calcifications.
   - D. Fluoroscopic imaging showing a "snowman" sign of dilated left colon split into 2 circles.
   - E. An "exclamation mark" appearance of the colon with a circular rectum with ascending colon appearing as a straight line without any rugae.

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5. A female term newborn infant is having her first physical examination and the clinician notes that it is difficult to visualize the anus, with a flat area without clear opening in the usual location. Which of the following are typically associated with imperforate anus?

   A. 22q11 deletion.
   B. Radiograph showing lack of air throughout the abdomen.
   C. Prenatal history of polyhydramnios.
   D. History of imperforate anus or Hirschsprung disease on both sides of the family.
   E. Ambiguous genitalia.

Anesthetic Exposure and Neurodevelopmental Outcomes in the Neonate

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Education Gaps

1. Animal studies have shown that anesthesia and sedative drugs administered during periods of rapid brain growth in early life can lead to widespread loss of nerve cells and long-term detrimental effects on learning and behavior. (1)(2)(3)
2. Neonates may be especially vulnerable to the cerebrovascular effects of hypotension and hypocapnia that occur commonly during general anesthesia.

Abstract

With ongoing advances in cardiorespiratory monitoring and improved anesthetic techniques, preterm and full-term infants routinely undergo successful surgical procedures under general anesthesia to repair congenital defects that were considered lethal in the past. Recent studies in immature animals exposed to anesthetics and sedative agents, however, have demonstrated clear evidence of neurotoxicity and deficits in learning that do not occur in older animals with the same exposure. Initial epidemiologic studies in humans also raised concern when it was found that children exposed to multiple anesthetics before age 4 years were more likely to demonstrate subsequent behavioral and learning deficits. Moreover, several recent case reports have highlighted concerns about the potential negative effects of intraoperative hypotension and hypocapnia on neonates undergoing anesthesia. Since 2009, the US Food and Drug Administration has been working collaboratively with the International Anesthesia Research Society in a public-private partnership called SmartTots to design and fund research to investigate these concerns. This review outlines the most recent evidence from both animal and human studies about the effects of anesthetic and sedative drugs and anesthetic-related hemodynamic changes on the developing newborn brain.

Objectives

After completing this article, readers should be able to:

1. Describe the extensive number of studies in young animals, including nonhuman primates, which led the Food and Drug Administration to issue

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ABBREVIATIONS

ASA	American Society of Anesthesiologists
EDI	Early Development Index
FDA	US Food and Drug Administration
GABA	γ-aminobutyric acid
IVH	intraventricular hemorrhage
LD	learning disability
MAP	mean arterial pressure
NIRS	near-infrared spectroscopy
NMDA	N-methyl-D-aspartate

a drug safety warning about the potential for anesthesia-related neurotoxicity in children younger than 3 years.

2. Explain the current data in humans that suggest that a single brief anesthetic in young children has no effect on subsequent neurodevelopment.
3. Recognize the potential negative sequelae of significant hemodynamic and respiratory perturbations encountered by neonates undergoing anesthesia.

INTRODUCTION

In December 2016, in a Drug Safety Communication, the US Food and Drug Administration (FDA) released the following statement: "The FDA is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains."(4) They further recommended: "Health care professionals should balance the benefits of appropriate anesthesia in young children and pregnant women against the potential risks, especially for procedures that may last longer than 3 hours or if multiple procedures are required in children under 3 years. Discuss with parents, caregivers, and pregnant women the benefits, risks, and appropriate timing of surgery or procedures requiring anesthetic and sedation drugs."(4) These recommendations followed 3 FDA advisory committee meetings between 2007 and 2014 and drew on an expanding literature of ex vivo, animal, and human data, drawing a link between anesthetic exposure and various aspects of brain development. (4) Given the strong responses from interested communities, the FDA published a subsequent drug safety communication in April 2017, clarifying that most of the data that prompted the first warning were based on animal studies and that necessary surgery should not be delayed or avoided. (5) This review details the current state of animal and human evidence relating to the effects of anesthesia, both pharmacologically and hemodynamically, on the developing brain.

ANESTHESIA AND THE NEONATE

Every year, thousands of preterm and newborn infants are exposed to general anesthesia during surgical procedures and imaging studies. More than 30 years ago, breakthrough studies by Anand and Hickey found that general anesthesia ameliorates the surgical stress response in infants and also decreases perioperative morbidity and mortality. (6) Shortly after the publication of this article, the Committee on Fetus and Newborn, the Committee on Drugs, the Section on Anesthesiology, and the Section on Surgery of the American Academy of Pediatrics published a joint policy statement that "local or systemic pharmacologic agents now available permit relatively safe administration of anesthesia or analgesia to neonates undergoing surgical procedures and that such administration is indicated according to the usual guidelines for the administration of anesthesia to high-risk, potentially unstable patients."(7)

While anesthesia and analgesia are essential for neonatal surgery, in this population, surgery continues to carry significant risk of morbidity and mortality. In 1961, the first major study of the rate of cardiac arrest during anesthesia demonstrated that infants younger than 1 year had the highest risk (1 in 700 from anesthesia alone). (8) Following decades of technological innovation and safer practice models, the risks have lessened but infants remain at higher risk than older children. Updated data demonstrate a rate of cardiac arrest under noncardiac anesthesia of 7 in 8,059 (1 in 1,151) for children younger than 1 year, 4 in 1,014 (1 in 253.5) for neonates (0–30 days old), and 19 in 80,580 (1 in 4,241) for children older than 1 year. (9) Therefore, compared with children older than 1 year, those less than a year of age were 3.7 times and neonates were 16.7 times more likely to suffer cardiac arrest. (9) An updated publication in 2007 from the Pediatric Perioperative Cardiac Arrest Registry demonstrated that 11% of perioperative cardiac arrests occurred in neonates (0–30 days old) and 38% occurred in children younger than 1 year. (10) In a more recent Australian study, the overall perioperative 24-hour mortality rate for children was 13.4 in 10,000 anesthetics, and the 30-day mortality was 34.5 in

10,000 anesthetics. (11) Neonates (0–30 days old) had the highest mortality of all of the pediatric age cohorts. (11)

ANESTHESIA-RELATED NEUROTOXICITY

Animal Data

Ever since the first animal study was published in 1999 suggesting that anesthetic agents may have a detrimental effect on the developing brain, (12) numerous additional studies have been conducted in immature animals of various species (including rodents, piglets, nematodes, and nonhuman primates) demonstrating evidence of anesthesia-related neurotoxicity. Two broad classes of medications have been shown to induce accelerated neuronal cell death (apoptosis): γ-aminobutyric acid (GABA) agonists (eg, benzodiazepines, propofol, and fluorinated anesthetics such as sevoflurane) and N-methyl-D-aspartate (NMDA) antagonists (eg, nitrous oxide and ketamine) (Table 1).

The first studies of this association were in rat pups that were found to have widespread neuroapoptosis after having combined exposure to midazolam and isoflurane (GABA agonists) as well as nitrous oxide (NMDA antagonist). (12) Though neuroapoptosis is a part of normal neurodevelopment and not inherently deleterious, the apoptosis observed in these rat pups was excessive and accompanied by deficits in learning and memory at later ages. (13) Accelerated apoptosis has been seen in immature animals after exposure to most anesthetic agents, including isoflurane, sevoflurane, halothane, thiopental, propofol, ketamine, nitrous oxide, and benzodiazepines. (14)(15)

A dose response to GABA agonists and NMDA receptor antagonists has also been observed in these studies, with greatest apoptosis occurring after longer exposures to higher doses and at younger ages (the late gestation/neonatal period in primates and <7 days in rat pups), a time of rapid brain development. (16) Subsequent studies have revealed additional evidence of anesthesia-related neuronal damage, including degeneration of mitochondria, (17) effects on neurogenesis, (18) altered dendritic spines, (19) decreases in trophic factors, (20) and impaired astroglial development. (21) Recent studies have also further delineated specific mechanisms inducing neurotoxicity (22) including neuroapoptosis with autophagic cell death, (23) alterations in cell migration, (24) and ketamine-induced neurotoxicity involving the PKC/ERK pathway (25) (Table 2).

Most concerning in these animal studies are the findings of sustained effects on learning and memory after prolonged anesthetic exposure. In nonhuman primates, long-term impaired learning and altered behavior have been demonstrated after prolonged ketamine exposure (24 hours of a “light surgical plane of anesthesia”). (26) Of particular note, though, when rat pups were placed in an enriched environment after anesthesia exposure, the long-term detrimental neurodevelopmental effects associated with neuroapoptosis could be prevented, suggesting that this neurologic deficit can be ameliorated. (27)

TABLE 1. **Anesthetic Agents Implicated in Increased Neuroapoptosis**

GABA AGONISTS	NMDA ANTAGONISTS
Benzodiazepines	Ketamine (Ketalar)
Midazolam (Versed)	
Lorazepam (Ativan)	
Propofol (Diprivan, Propovan)	Nitrous oxide
Etomidate (Amidate, Hypnomidate)	
Fluorinated volatile anesthetics	
Isoflurane (Forane, Terrell)	
Sevoflurane (Ultane, Sojourn, Sevorane)	
Halothane	
Desflurane (Suprane)	
Barbiturates	
Thiopental[a]	
Pentobarbital (Nembutal)	
Methohexital (Brevital)	

Common brand names in parenthesis. GABA=γ-aminobutyric acid; NMDA=N-methyl-D-aspartate.

[a] Not commercially available in the United States. All others are associated with a Food and Drug Administration warning.

TABLE 2. **Neurologic Injuries Noted after Anesthetic Exposure in Infant Animals**

- Neuroapoptosis (rodents, nonhuman primates, nematodes)
- Alterations in dendritic spines (rodents)
- Altered neurogenesis (rodents)
- Impaired astroglial development (ex vivo rodent cultures)
- Mitochondrial degeneration (rodents)
- Decreases in trophic factors (rodent primary neurons)
- Cognitive deficits (nonhuman primates)
- Memory and learning (rodents)

Several agents conferring some degree of neuroprotection that are also actively being studied, including dexmedetomidine (alpha-2 agonist), have been shown to both protect against and reverse anesthetic-induced neurotoxicity in animals. (28) Newer studies are specifically investigating the mechanisms linking pharmacologic insult to functional deficits. (29) The hope is that as these mechanisms are better understood, preventive and postexposure interventions can be used to minimize the impact of anesthetic neurotoxicity.

However, translating animal studies to humans is fraught with difficulties, not the least of which is the tremendous difference in brain complexity in humans as well as the longer natural life span. Study medications in animal models are generally introduced at far higher than clinical doses per body weight, for relatively longer periods, and generally not accompanied by rigorous hemodynamic monitoring. This is important because it is likely that the immediate and long-term impact of hemodynamic perturbations may also increase the vulnerability to the neurotoxic effects of anesthetic agents.

Human Data

The period of fastest brain growth in humans occurs between 28 weeks' gestational age and 24 months' chronologic age. Human studies, therefore, have focused on children who received anesthetic and sedative agents before age 4 years. The initial studies were small epidemiologic studies demonstrating an increased incidence of learning deficits in children who had more than 1 anesthetic exposure before age 4 years. Subsequent studies evaluated larger longitudinal cohorts and controlled for medical and environmental exposures. The results of these studies have been mixed, with some studies showing an association between early (age <2–4 years, depending on the study) anesthetic exposure and subsequent neurodevelopmental concerns, and some more recent studies showing minimal or no impact (Table 3).

In 2009, using an epidemiologic cohort of ~5,000 children in Rochester, MN, born between 1976 and 1982 (593 receiving anesthesia before age 4 years), Wilder and colleagues demonstrated no significant neurodevelopmental impact (in the form of learning disabilities [LDs]) from a single anesthetic encounter, but increased risk with 2 or more anesthetics. (30) They did not control for comorbid illness, but statistical subanalysis showed no impact of American Society of Anesthesiologists (ASA) physical status on LDs in the 144 children who received multiple anesthetics. (30) An oft-cited limitation of this particular study is that the primary agent used to anesthetize these children is no longer commercially available in the United States because of its negative cardiovascular effects. (30) A study of Medicare records of 383 children (with 5,050 frequency matched controls) undergoing inguinal herniorrhaphy before age 3 years in New York demonstrated a greater than 2-fold increase in LDs in exposed children. (31) However, a monozygotic twin study from Bartels et al in the Netherlands failed to demonstrate neurodevelopmental or intellectual differences between exposed and nonexposed twins in twin-pairs. (32)

With these initial population and cohort studies yielding discrepant findings, it was clear that larger prospective and controlled studies were needed to determine whether human infants undergoing anesthesia demonstrated the same characteristics as immature animals exposed to anesthesia. Without prospective analysis, it is impossible to demonstrate clear causation, only association. Recent studies have specifically controlled for factors that are known to have a significant impact on neurodevelopmental and educational outcomes such as maternal education and comorbid illness.

In 2016, the largest cohort study using detailed neurodevelopmental testing was published: the multicenter Pediatric Anesthesia and Neurodevelopmental Assessment study. Using full-scale IQ as the primary outcome, closely age-matched (<36 months' difference in age) sibling cohorts, in which 1 sibling received anesthesia for hernia repair before age 3 years, were assessed at 8 to 15 years of age. (33) They found no significant difference between the groups in IQ (or subscale of IQ) or behavior. (33) To control for comorbid illness as a confounder, they excluded children who were classified as ASA physical status class III or above (ie, patients with severe systemic disease) as well as premature infants (estimated gestational age <36 weeks). The authors speculated that similar confounders may have accounted for prior data demonstrating an association. (33)

Also published in 2016 was the first randomized controlled trial investigating human anesthetic neurotoxicity: the General Anesthesia and Awake-Regional Anesthesia in Infancy study. (34) The patient population included 722 infants undergoing hernia repair at multiple centers spanning 3 continents. They were randomized to receive either general anesthesia or awake-regional anesthesia (spinal or caudal), with the primary outcome measure being the evaluation of the Wechsler Preschool and Primary Scale of Intelligence–Third Edition Full Scale IQ at 5 years of age. Though the final results of this study will not be complete until after 2018 when all subjects have reached age 5 years, secondary outcomes of the Bayley-III examination

TABLE 3. **Select Studies Correlating Early Anesthetic Exposure to Neurocognitive Development in Human Subjects**

YEAR	STUDY	POPULATION	FINDINGS	CONTROL FOR COMORBID ILLNESS
2009	Wilder et al (Mayo Clinic, MN)	Epidemiologic cohort (5,000 children)	Increased risk of learning disabilities with multiple anesthetics (no difference with single anesthetic).	No nonanesthesia exposure control cohort. Subanalysis excluding ASA PS III and above did not alter outcomes.
2009	Bartels (Netherlands)	Monozygotic twin pairs	Similar intellectual attainment between twins who did and did not receive anesthesia.	Exclusion based on prematurity. Twins who did not receive anesthesia served as controls for their siblings who did.
2016	Graham (Canada)	Canadian cohort	Early anesthesia and Early Development Index weakly associated, but only for those exposed after age 2 y. No increased risk with multiple anesthetics.	Children with developmental disabilities excluded. Used Johns Hopkins Resource Utilization Bands as covariates in mixed logistic regression models to account for severity of comorbid illness.
2016	PANDA study (multicenter)	Sibling pairs undergoing hernia repair before age 3 y	No differences in performance and verbal subscales of the IQ; no differences in motor speed, processing speed, visuospatial, language, attention, and executive function; no differences in behavior.	Only included ASA PS I and II and those born ≥36 weeks' GA.
2016	GAS study (multicenter, international)	Infants undergoing hernia repair (randomized to general anesthesia or regional only)	Primary outcome at 5 y, follow-up pending (2018). Secondary outcome at 2 y, follow-up shows no difference in the composite cognitive score (adjusted for gestational age at birth).	Infants born premature (≥26 weeks' GA) included, but those with "existing risk factors for neurologic injury" excluded (eg, congenital heart disease, recent mechanical ventilation, prior neurologic injury).
2017	Glatz (Sweden)	Swedish cohort (2.17 million children)	Primary outcomes: School grades at age 16 y, IQ at military inscription at age 18 y. Group with single exposure before age 4 y had 0.41% lower grades and 0.97% lower IQ. No further impact from multiple exposures.	Contextualized results by comparing with impact of sex, month/year of birth, and maternal education level on primary outcomes and found anesthetic exposure had far smaller impact than these factors. Excluded children with hospitalizations subsequent to anesthetic exposure as control.
2018	MASK study (Mayo Clinic, MN)	Birth cohort of children singly, multiply, and nonexposed to anesthesia <3 y of age.	Fine motor and processing speed decreased in multiply exposed group. No difference in IQ between groups. Subjective parental report of behavior, reading, and executive function problems in multiply exposed group.	Groups propensity matched based on rigorous health data variables (using the Johns Hopkins Adjusted Clinical Group Case Mix System), GA at birth, birthweight, Apgar scores, and parental age and education level.

This list includes notable articles in this field and is not intended to be exhaustive of all data. ASA=American Society of Anesthesiologists; GA=gestational age; PS=physical status (class I=healthy patient; class II=mild systemic disease; class III=severe systemic disease).

at age 2 years show no differences between the groups after adjusting for gestational age at birth. (34) Though the duration of the anesthetic in this study was brief (mean, 54 minutes), the preliminary results suggest that a single brief exposure to anesthesia does not significantly affect early neurodevelopment. (34)

Two recent large longitudinal studies have suggested a weak association between early exposure to anesthesia and neurotoxicity. The first was a retrospective matched cohort study of Canadian children that sought to determine the impact on school readiness (Early Development Index [EDI]) of a single general anesthetic before age 4 years. (35) They found only a weak association between poorer EDI and anesthetic exposure and only for children exposed to anesthesia between 2 and 4 years of age (after controlling for age, gestational age at birth, and socioeconomic factors). (35) In contrast to previous studies, they also found no association between multiple anesthetics and EDI. (35)

In 2017, a large retrospective Swedish cohort study of 2.17 million children sought to investigate the impact of a single anesthetic on neurodevelopment in otherwise healthy children. (36) Their cohort included 33,514 children born between 1973 and 1993 who received a single anesthetic before age 4 years with no subsequent hospitalizations (presumably controlling for significant comorbid illness). They also identified 3,640 children who received multiple anesthetics before age 4 years. The primary outcomes were the school grades at age 16 years and the IQ test score at the time of military conscription at age 18 years. They found a small difference in school grades at age 16 years (0.41% lower, 95% confidence interval, 0.12-0.70%) and a 0.97% lower IQ (95% confidence interval, 0.15-1.78%) at 18 years after exposure in early life, regardless of the number of exposures. Despite finding a statistically significant difference, the authors noted that this difference was less than the difference in IQ seen with year and month of birth, maternal education level, and gender, and advised that neurodevelopment is much more influenced by "environmental, medical, and individual factors" than anesthetic exposure. (36)

Most recently, the Mayo Anesthesia Safety in Kids study was published with the primary hypothesis that multiple, but not single, anesthetic exposures predisposed children to subsequent neurodevelopmental deficits. (37) They studied children born in Olmstead County, MN, between 1994 and 2007. In all, nearly 1,000 children completed testing at ages 8 to 12 years or 15 to 20 years; of these, 411 children had no exposures, 380 had single exposures, and 206 were exposed to anesthesia multiple times before age 3 years. (37) There was no statistically significant difference in IQ between the 3 groups, but children having multiple exposures had worse fine motor skills and processing speed. Subjectively, parents of children with multiple exposures reported more concern with behavior, reading, and executive function. (37) These data further bolster the supposition that a single brief anesthetic exposure does not cause significant neurodevelopmental damage but leaves the question open as to whether multiple or longer anesthetic exposures may lead to some degree of neurotoxicity.

Anesthesia-Related Hemodynamic Perturbations

Recent case reports of brain injury related to intraoperative hypotension and hypocapnia in infants have led some anesthesiologists to speculate that intraoperative hemodynamic changes and ventilatory issues may have detrimental neurodevelopmental effects in vulnerable infants. Improved methods of neuromonitoring have shed new light on the specific neurovascular vulnerabilities in the neonatal brain related to hemodynamic and metabolic perturbations.

Hypotension and Cerebral Autoregulation in Neonates

A case series by McCann et al in 2014 was the first to highlight concerns regarding perioperative hypotension as a cause of postoperative neurologic deterioration. (38) The authors described 6 infants of less than 48 weeks' postmenstrual age who developed postoperative encephalopathy attributable to cerebral hypoperfusion. All patients had new-onset seizures within 25 hours of anesthetic administration and were found to have cerebral pathology manifesting as supratentorial watershed infarction in the border zone between the anterior, middle, and posterior cerebral arteries. (38) A detailed review of the intraoperative records revealed that during each anesthetic administration, most of the systolic blood pressure values measured during the procedure were less than 60 mm Hg. Four of the six infants also had prolonged periods of mild hypocapnia (<35 mm Hg). Follow-up of these infants found that 2 had normal neurologic examination findings, 1 had minor motor delays, 1 had profound developmental delays, 1 had died, and 1 was lost to follow-up. (38)

Normal blood pressure values for infants are variable but are most correlated with an infant's postmenstrual age (ie, lower for preterm than full-term infants). In full-term infants, blood pressures are generally lower on the first day after birth (mean systolic blood pressure, 62.6 mm Hg) and increase by approximately 9% at 36 hours of age. By the end of the first week of age, awake term infants have a normal blood pressure, with an average of 71.8/50.5 mm Hg for girls and 72.7/51.1 mm Hg for boys. (39)(40) These values increase slightly until 6 weeks of age and then remain fairly stable until age 1 year. The definition of neonatal hypotension is a mean arterial pressure (MAP) that is below the 5th or 10th percentile for gestational and postnatal age. (41) The consensus statement of the Joint Working Group of the British Association of Perinatal Medicine in 1992 recommended that clinicians should prevent an infant from having an MAP that is below the infant's gestational age in weeks (approximately the 10th percentile for age). (42) A more recent study suggested that the absolute lower limit for mean blood pressures should be 30 mm Hg in infants of less than 30 weeks' postmenstrual age. (43)

Most experts recommend that the MAP be maintained within the limits of cerebral autoregulation to optimize cerebral protection. For infants with open fontanelles, once the limits of cerebral autoregulation are reached, cerebral perfusion pressures will vary directly with arterial blood pressure. Unfortunately, the lower limits of autoregulation in neonates are not precisely known.

Cerebral oxygenation, as measured with near-infrared spectroscopy (NIRS), is more affected by decreases in MAP in infants younger than 6 months than in older infants. (44)

Several studies have specifically examined the lower limits of autoregulation under sevoflurane anesthesia in young children. The first of these studies published in 2003 showed that infants younger than 6 months demonstrated a lower limit of autoregulation at a MAP of 38 mm Hg, a 20% decrease from baseline in the awake state compared with a 40% reduction in infants older than 6 months. (45) A subsequent study using both transcranial Doppler and NIRS demonstrated that cerebral blood flow decreases when the MAP falls below 35 mm Hg in infants younger than 6 months. (46) These reports suggest that infants most likely have a decrease in cerebral autoregulatory reserve and are at greater risk of insufficient cerebral perfusion during general anesthesia.

Most general anesthetics are associated with some degree of hypotension related to peripheral vasodilation that is ameliorated by intravenous fluids and surgical stimulation. However, young infants undergoing major surgeries may have prolonged periods with minimal painful stimulation during intravenous line placement, neuraxial blocks, and surgical preparation, which may increase the risk for protracted periods of hypotension. Insufficient cerebral perfusion following significant hypotension can lead to partial ischemia and potentially injure the watershed areas between major cerebral blood vessels, the same areas that were found to be affected in the case series by McCann et al. (38)

General anesthesia in adults decreases cerebral metabolic rate and oxygen demand. Concern has been raised that this may not be true for infants. Most anesthetic agents are GABA receptor agonists, which have inhibitory effects in the mature brain but may be excitatory in the developing brain. (47) Term infants begin to develop a more inhibitory response to GABA receptor agonists at approximately 15 weeks' postnatal age. A recent study in infants demonstrated that cerebral oxygenation increases with the administration of sevoflurane anesthesia. Associated intraoperative decreases in MAP, however, had a more detrimental effect on brain oxygenation in infants younger than 6 months than in older children. (44)

Hypocapnia and Brain Perfusion

The partial pressure of arterial carbon dioxide (Paco_2) is also an important modulator of cerebral blood flow because of its vasoactive effect on cerebral arteries. Hypocapnia causes cerebral vasoconstriction and decreased cerebral blood flow. Recent studies have demonstrated that neonates, especially preterm infants, may be particularly vulnerable to this hypocapnia-induced brain ischemia. (48) A single-center retrospective review of clinical and blood gas data in very-low-birthweight neonates in the first 4 days after birth suggested that infants who had persistently low or high Paco_2 values had a higher rate of severe intraventricular hemorrhage (IVH). Neonates with a maximal Paco_2 value less than 39 mm Hg (5.2 kPa) had a 27% incidence of severe IVH and those with both maximal Paco_2 values greater than 60 mm Hg and minimal Paco_2 values less than 39 mm Hg (5.2 kPa) had a 38% incidence of severe IVH. This is comparable to infants whose maximal Paco_2 measurements were in the "optimal" range of 39 to 60 mm Hg (5.2–8 kPa) who were found to have a 3% incidence of severe IVH. (49) In a randomized trial of whole-body cooling in infants of more than 36 weeks' gestational age with encephalopathy, infants who had either a minimum Paco_2 or cumulative Paco_2 less than 35 mm Hg (4.7 kPa) had poorer outcomes. (50) Hypocapnia (defined as Paco_2 <35 mm Hg [4.7 kPa]) was also found to be an identified risk factor for cystic periventricular leukomalacia in preterm infants. (51) Although capnography is a standard anesthesia monitor, end-tidal carbon dioxide measurements in low-birthweight infants or those with severe lung disease may not correlate well with actual Paco_2 values. Capillary blood gas or arterial measurements, therefore, may be particularly important in vulnerable infants to prevent prolonged intraoperative hypo- or hypercapnia.

OVERSIGHT AND ADVANCEMENT

If a baseball player turned away after every hit without seeing where the ball landed, the player would not likely improve. So too must be the practice of anesthesia. Bringing a child safely through an anesthetic is like hitting a baseball, but without knowing how that child develops after their anesthetic, we cannot improve care of subsequent patients.

With the efforts of SmartTots, a public-private partnership between the FDA and the International Anesthesia Research Society, significant resources are currently being allocated to the study of the impact of anesthesia on the developing brain. Key future directions in this research include preclinical dose-response relationships to neurotoxicity, comparisons of drugs that mitigate neurotoxicity, and specific "translatable" biomarkers. Inflammation and inflammatory markers are another key area of interest, because neurotoxicity is felt to be exacerbated in an inflammatory environment. (52) With the collective resources, expertise, and data emanating from these organizations, it is hoped that in the near future we will be able to gain a greater understanding of the impact of anesthesia on the developing brain. In addition, it may improve our ability to provide anesthesia that is well-tolerated hemodynamically but has minimal long-term neurodevelopmental effects.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the effects of variations in arterial and venous blood pressure, blood gas tensions, and hemoglobin concentration on cerebral blood flow and cerebral vascular resistance and cerebral perfusion.

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Index of Suspicion in the Nursery

1 Periorbital Swelling and Conjunctivitis in a Preterm Infant

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AUTHOR DISCLOSURE Drs Newman, Horan, and Kurtom have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A preterm male infant is born at 34 weeks of gestation to a 30-year-old gravida 1, para 0 woman with no significant medical history and good prenatal care. The family medical history is not significant. Prenatal serologic tests for syphilis, human immunodeficiency virus, and hepatitis B are negative and rubella status is immune. She develops gestational hypertension for which she undergoes antepartum observation for 3 weeks. After her condition progresses to preeclampsia with severe features, the decision is made to induce delivery. She receives antenatal corticosteroids and magnesium sulfate before delivery, as well as 5 doses of ampicillin for unknown group B *Streptococcus* status. The infant had been depressed at birth, with postresuscitation Apgar scores of 1, 5, and 8 at 1, 5, and 10 minutes, respectively. He is noted to have respiratory distress secondary to mild respiratory distress syndrome, is given noninvasive positive pressure ventilation, and begins empiric treatment with ampicillin and gentamicin after a blood culture specimen is collected. Initial laboratory findings, including complete blood cell count and electrolytes, are unremarkable. After 2 days, he makes a transition to a simple nasal cannula with room air, and oral feeds are started. Antibiotics are stopped after 2 days because blood cultures show no growth. After 4 days, he is noted to have temperature instability and apnea. Because of a concern for sepsis, blood and cerebrospinal fluid culture specimens are drawn and he is restarted on ampicillin and gentamicin treatment. The following day, the blood culture shows gram-negative rods and cefepime is added to his treatment regimen. On the 6th day after birth, he is noted to have periorbital swelling and erythema of the left eye with purulent drainage, conjunctivitis, and grey discoloration of the cornea. Ophthalmology consultation finds a large corneal infiltrate and corneal swelling (Fig). Two-dimensional (2D) mode ultrasonography is performed, which demonstrates diffuse vitreous haze along with a large retinal attachment. Culture specimen of the vitreous humor obtained during surgery confirms the diagnosis.

DIAGNOSIS

The differential diagnosis for a red, swollen eye in a newborn is broad. However, the combination of sepsis, clinical or culture proven, and noted hypopyon are suspicious for endopthalmitis. Given the lack of visibility of the anterior and posterior chambers on examination, 2D ultrasonography is indicated to evaluate the extent of infection. Magnetic resonance imaging was subsequently obtained,

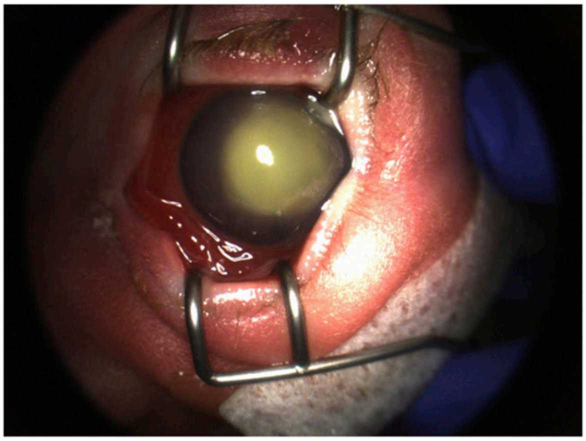

Figure. A large corneal infiltrate is seen, which appears to be of full thickness and encompasses approximately 60% to 70% of the corneal surface area. Surrounding corneal edema can be seen. The pupil and lens are not visible.

which showed diffuse enlargement of the globe, posterior displacement of the lens, and retrobulbar soft tissue enhancement. Given the risk of globe rupture and sympathetic opthalmia, the decision was made to perform evisceration with subsequent placement of an acrylic implant. Specimens of the initial blood culture as well as of the vitreous taken after surgery were positive for *Serratia marcescens*, confirming the diagnosis of endogenous endophthalmitis. He received cefepime for a total of 21 days. The right eye was treated prophylactically with tobramycin ophthalmic solution. The infant was discharged 1 week later.

DISCUSSION

Neonatal endogenous endophthalmitis is a rare, potentially devastating infection of the inner eye, caused by hematogenous spread of pathogenic microorganisms. In the Unites States, its incidence has been decreasing at a rate of 6% per year. In 2006, 4.42 cases per 100,000 live births were reported. (1) The most common cause of endophthalmitis in newborns is fungal, secondary to candidemia. Group B *Streptococcus*, *Pseudomonas*, and other gram-negative rods account for the majority of bacterial infections. Transmission can occur vertically at the time of delivery, as is likely in the current case, or from contaminated catheters or respiratory equipment. (2) *S marcescens,* a rare cause of neonatal endophthalmitis, is mentioned only 5 times in the literature. (3)(4)(5)(6)(7) Associated risk factors are generally those seen frequently in preterm infants, including those with birthweights less than 1,500 g, candidemia, systemic bacteremia, retinopathy of prematurity, blood transfusion, respiratory disorders, and perinatal infections. (1) It is hypothesized that the persistence of the tunica vasculosa lentis makes preterm infants uniquely susceptible. (2)

Bacterial endophthalmitis frequently presents with lid edema, conjunctival injection, corneal edema, and exudates in the anterior chamber. (8)(9) Pink hypopyon is a rare physical examination finding that may be seen with *Serratia* endophthalmitis, because of bacterial production of the pigment prodigiosin. (5)(9) Loss of the red reflex itself can be an early sign of endopthalmitis, as can conjunctivitis. The presence of a red eye or lack of a red reflex in any patient with sepsis should prompt full ophthalmologic evaluation. It is therefore recommended to examine the conjunctiva and red reflex of any newborn with signs of sepsis. Any concerning findings should prompt an immediate ophthalmology consultation. Diagnosis is made clinically based on anterior chamber findings or vitreous opacities. (2) Culture specimens from both the aqueous and vitreous humor should be sent, in addition to blood cultures to determine sensitivity to antibiotics. Treatment includes broad-spectrum systemic and intravitreal antibiotics. Outcomes are poor, and infection may result in evisceration or enucleation.

Lessons for the Clinician

- Ophthalmologic examination should be performed in all newborns to evaluate the conjunctiva, iris, and red reflex.
- Loss of the red reflex in an infant with sepsis may be an early sign of endophthalmitis.
- Ophthalmology should be consulted early for any suspected ocular infection.
- All suspected cases should be treated with broad-spectrum antimicrobials initially.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes and clinical and laboratory features of acute neonatal infections of the eyes, including ophthalmia neonatorum.

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2 Metabolic Alkalosis in a Neonate 12 Hours after Birth

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AUTHOR DISCLOSURE Drs Tergestina, Chandran, and Kumar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male infant is born at 36 weeks of gestation with a birthweight of 1,780 g. The mother is not noted to have pregnancy-induced hypertension or gestational diabetes mellitus. Dating scan corresponds to the gestational age calculated from date of the last menstrual period. The anomaly scan is normal. A third scan notes that at a gestational age of 36 weeks, biparietal diameter corresponds to 34 weeks, femur length corresponds to 33 weeks, and the abdominal circumference corresponds to 28 weeks. Amniotic fluid index is 9 cm; umbilical artery Doppler images are normal. In view of the intrauterine growth restriction, 1 dose of steroids (betamethasone 12 mg) is given. Labor is induced; however, the cardiotocograph shows a basal heart rate of 150 beats/min, variability of 10 beats/min, no accelerations, and spontaneous decelerations to 100 beats/min, with recovery over 2 minutes. The infant is delivered via lower-segment cesarean with Apgar scores of 9 and 9 at 1 and 5 minutes after birth, respectively. In view of the low birthweight, the infant is transferred to the neonatal unit. Anthropometric measurements at birth are as follows: weight, 1,780 g (<3rd percentile); length, 44 cm (10th percentile); and head circumference, 31 cm (10th percentile). In view of the unexplained intrauterine growth restriction, it is planned to evaluate the infant for an intrauterine infection and he is started on expressed breast milk feeds via paladai (an Indian enteral feeding device).

At 12 hours after birth, the infant is noted to have an episode of apnea—cessation of breathing for approximately 30 seconds in association with desaturation. This recovers on stimulation. However, his breathing continues to be shallow and the respiratory rate is 30 to 40 breaths/min. Suspecting sepsis, a blood culture is performed and treatment with antibiotics (penicillin and gentamicin) is started. Chest radiography, echocardiography, and neurosonography findings are normal. An arterial blood gas measurement shows metabolic alkalosis, with a pH of 7.71, bicarbonate 43.4 mEq/L (43.4 mmol/L), and base excess +19.9 mmol/L. Partial pressure of arterial carbon dioxide ($Paco_2$) is 33.2 mm Hg (4.4 kPa).

DISCUSSION

Diagnosis

The blood gas measurement was repeated to confirm the presence of metabolic alkalosis. It was also reconfirmed that the infant had neither repeated episodes of vomiting nor multiple stools. The infant was also not receiving any medication. He passed urine twice in the preceding 12-hour period.

Investigations showed a sodium concentration of 133 mEq/L (133 mmol/L) and magnesium of 1.81 mEq/L (0.91 mmol/L). Serum potassium and chloride values were 2.9 mEq/L (2.9 mmol/L) and 85 mEq/L (85 mmol/L), respectively. There was no evidence of hypercalciuria, with a urine spot showing a calcium-creatinine ratio of 0.04. Urine pH was 8.38 and urine chloride was 11 mEq/L (11 mmol/L). Invasive blood pressure monitoring via radial arterial line showed pressures that were normal for gestational age. Ultrasonography of the kidneys and electrocardiography were performed, both of which had normal findings.

Maternal history included 4 admissions in the course of the pregnancy for hyperemesis gravidarum. Her history included approximately 20 episodes of vomiting per day. She was also evaluated by a gastroenterologist and surgeon for suspected subacute intestinal obstruction and pancreatitis, and by a psychiatrist for depression, psychosis, and an eating disorder; however, all evaluations were found to be negative. The mother was treated symptomatically with doxinate (doxylamine + pyridoxine hydrochloride tablet), ondansetron, and pantoprazole. The episodes of vomiting continued until delivery, with a 16-kg weight loss throughout the pregnancy. Maternal blood gas was measured at this point, and showed a pH of 7.6 and bicarbonate of 34.14 mEq/L (34.14 mmol/L).

Hospital Course

The infant was treated with normal saline boluses and potassium supplementation. His blood gas values normalized on day 4 after birth, and bicarbonate concentrations reached normal levels by day 5. Serum potassium was 3.3 mEq/L (3.3 mmol/L) at 48 hours after birth. Investigations for sepsis and intrauterine infections had negative findings. Feedings that were stopped on day 1 when the infant developed shallow breathing and apnea were restarted on day 2. Intravenous fluids were tapered as feeds increased, and were stopped on day 4. The infant started breastfeeding on day 4, and was discharged on exclusive breastfeeding.

The Condition

Metabolic alkalosis is characterized by a primary increase in serum bicarbonate concentration such as to increase the pH to more than 7.45. In the neonate, this is most commonly secondary to hydrogen ion (H+) losses as seen in vomiting/continuous nasogastric aspiration, congenital chloride-wasting diarrhea, renal losses such as Bartter syndrome, or endocrine causes such as congenital adrenal hyperplasia or hyperaldosteronism. Other causes of metabolic alkalosis are secondary to diuretic (loop or thiazide) administration or inadvertent iatrogenic administration of bicarbonate or its sources. Metabolic alkalosis in the fetus is described secondary to excessive and prolonged vomiting and diarrhea and long-term administration of diuretics and prostaglandin E in the mother, leading to a hypochloremic metabolic alkalosis in the neonate. While the placenta acts as a clearinghouse for all metabolic disorders in the fetus, persistent alkalemia in the mother leads to increased transport of bicarbonate across the placenta, resulting in fetal alkalosis.

The physiologic effects of an elevated pH level are many. The respiratory drive can be inhibited via the central and peripheral chemoreceptors. This can present in the neonate as hypoventilation and apnea. Decreased myocardial contractility and arrhythmias and a secondary hypokalemia are well described. In the brain, alkalosis leads to cerebral vasoconstriction, and symptoms of lethargy and occasionally neuromuscular excitability and seizures.

Maternal weight loss secondary to hyperemesis gravidarum is described as a causative factor for intrauterine growth restriction. In addition to hyperemesis, long-term use of laxatives and diuretics and an eating disorder have also been described as causative for a pseudo–Bartter syndrome. The metabolic alkalosis, abnormal electrolytes, and weight loss in the mother in the current case resolved after delivery. The persistent maternal alkalosis led to a fetal metabolic alkalosis, which persisted after birth in the newborn.

Bartter syndrome is characterized by antenatal polyhydramnios, and postnatal features of a characteristic facies and hypokalemic metabolic alkalosis with increased urinary chloride excretion. The absence of the antenatal features, facies, and decreased urinary chloride levels differentiate this from Bartter syndrome. Aside from the classic history of recurrent gastrointestinal losses and metabolic alkalosis in the mother, the resolution of symptoms by days 4 to 5 also helped differentiate this from Bartter syndrome.

Historically, in 1979, infants fed with chloride-deficient soy formula developed hypochloremic metabolic alkalosis. Follow-up of these infants 9 and 10 years later found that their cognitive development appeared to be normal; however, these children were at risk of developing expressive language skill deficits. Follow-up of an infant with metabolic alkalosis in a mother with an eating disorder showed normal neurodevelopmental outcome at 2 years.

MANAGEMENT

The infant described here was treated with normal saline boluses given as infusions of 10 mL/kg. Potassium was added in the intravenous fluid at 3 mEq/kg per day. It was expected that restoration of effective arterial volume would correct the chloride deficit and increase renal sodium bicarbonate excretion.

Reduced arterial blood volume leads to persistence of alkalosis as the kidneys conserve sodium, limiting the excretion of bicarbonate. Hypokalemia leads to increased proximal tubular bicarbonate reabsorption, and activation of hydrogen-potassium-adenosine phosphatase in the collecting tubules, which acts to reabsorb potassium in exchange for hydrogen ions. This leads to increased bicarbonate reabsorption and maintenance of the alkalemia. Supplementation of potassium leads to the intracellular movement of potassium in exchange for the movement of hydrogen ions into the extracellular fluid, which buffers the bicarbonate.

Lessons for the Clinician

- Metabolic alkalosis on day 1 in a neonate is usually secondary to a maternal cause.
- Treatment is via infusion of normal saline and supplementation of potassium chloride.
- Although the metabolic alkalosis resolves by days 4 to 5, long-term neurodevelopmental outcome is unknown.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants.

Suggested Readings

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3 A Term Newborn with Intrauterine Growth Restriction and Severe Fetal Brain Anomalies

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AUTHOR DISCLOSURE Drs Biobaku, Babata, Friedman, Goddard, and Yen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 29-year-old gravida 4, para 3 woman is seen by the maternal-fetal medicine team because of abnormal ultrasonographic findings at 34 weeks of gestation. The fetus has severe intrauterine growth restriction (IUGR) (<1st percentile) and multiple organ abnormalities, including microcephaly, small forebrain, scalloped parietal bones, bilateral ventriculomegaly, dilated third ventricle, splayed thalami, irregular falx, scattered intracranial calcifications, and a small, flattened forehead. Fetal echocardiography shows levorotation of the cardiac axis, tortuous ductus arteriosus, and tricuspid valve thickening.

Her prenatal history is notable for travel to the Dominican Republic until 12 weeks of gestation. She denies any fever, insect bites, rash, conjunctivitis, or arthralgia. Findings on other prenatal laboratory screening are reassuring.

After the induction of labor for IUGR, a male infant is delivered at 37 2/7 weeks of gestation via normal spontaneous vaginal delivery. Brief positive pressure ventilation is given in the delivery room for an initial low heart rate. The heart rate quickly recovers, but respiratory distress develops, requiring continuous positive airway pressure (CPAP). The infant is transferred to the NICU with the administration of CPAP.

Upon admission, physical examination shows a boy with a birthweight of 2,140 g (2.8th percentile), length of 40.5 cm (<1st percentile), and head circumference of 29 cm (<1st percentile). Pertinent findings include microcephaly and global hypertonia, along with contractures of the upper and lower extremities (Fig 1).

DISCUSSION

Symmetric IUGR often results from intrinsic fetal factors, with an extensive differential diagnosis that includes:

- Chromosomal abnormalities
- Congenital infections (*t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, *h*erpes simplex, *Z*ika virus [TORCH-Z])
- Inborn errors of metabolism

Chest radiography shows paralysis of the right hemi-diaphragm (Fig 2). Complete blood cell count, blood cultures, urine cytomegalovirus shell vial assay, and newborn screening for toxoplasmosis all had negative results. Given the extensive brain malformations, genetic and endocrine evaluations were performed. The karyotype was 46,XY. Cortisol, free thyroxine, luteinizing hormone,

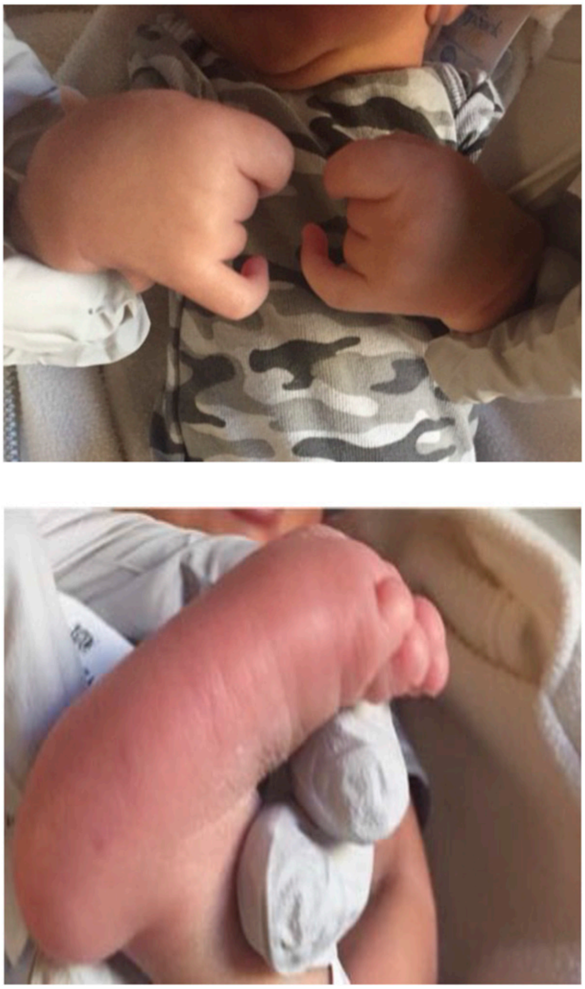

Figure 1. Contractures of upper and lower extremities.

and follicle-stimulating hormone concentrations were all normal. A Zika virus diagnostic panel was sent and included:

- Maternal placenta for Zika virus RNA
- Maternal urine and serum Zika virus RNA
- Infant's blood for Zika virus immunoglobulin M (IgM) with confirmatory plaque reduction neutralizing antibody test (PRNT)
- Infant's urine and serum Zika virus RNA

Postnatal echocardiography revealed no structural abnormalities in the infant. Ophthalmologic evaluation was within normal limits. He did not pass his hearing screen. Ultrasonography of the hip demonstrated developmental dysplasia.

Diagnosis and Further Progress

The infant was gradually weaned from CPAP to nasal cannula. A postnatal magnetic resonance imaging (MRI) scan (Fig 3) revealed microcephaly, pachygyria, partial agenesis of the corpus callosum, ventriculomegaly, vermian hypoplasia, and parenchymal calcifications. He was discharged from the hospital with full oral feeds and a nasal cannula.

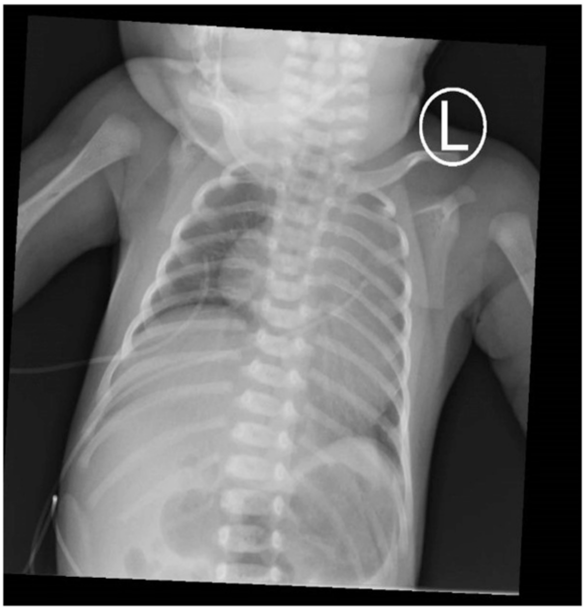

Figure 2. Chest radiograph showing right hemi-diaphragm paralysis.

Zika virus RNA returned positive for the placenta, but the mother's urine and serum samples were negative, as were the infant's urine and serum samples. Infant's Zika virus IgM was initially inconclusive, but the confirmatory PRNT result was positive for Zika virus and dengue. Based on the Centers for Disease Control and Prevention guidelines, the infant was considered presumptive positive for congenital Zika virus syndrome.

Audiology follow-up revealed moderate to severe hearing loss necessitating hearing aids. Ankle contractures and hypertonia required serial casting. He was seen by a pulmonologist who managed his nasal cannula support, with a plan to perform ultrasonography to further evaluate the hemi-diaphragm paralysis.

The Condition

The prenatal ultrasonographic findings, travel history, postnatal MRI, and positive Zika virus PRNT result are consistent with congenital Zika virus syndrome. Zika virus infection is a new teratogenic disease caused by the mosquito-borne flavivirus. Our knowledge of the congenital Zika virus syndrome is still evolving. (1) Zika virus causes direct cellular injury to the central nervous system with the live virus identified in brain tissues of

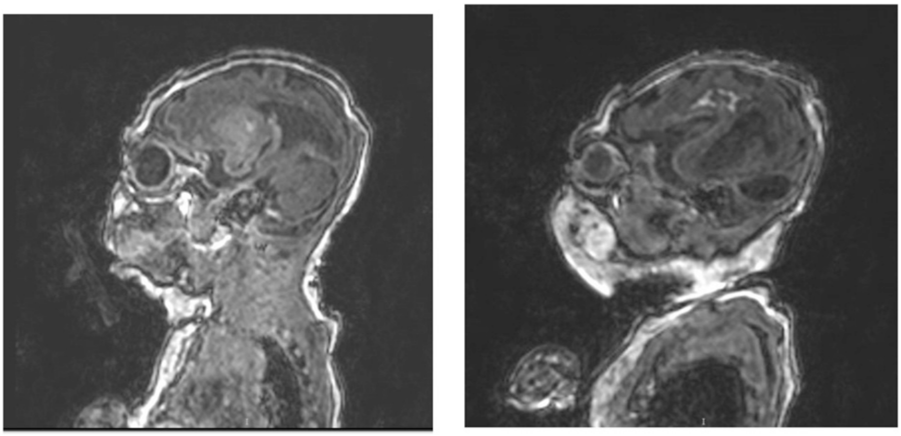

Figure 3. Postnatal magnetic resonance imaging scan showing microcephaly, pachygyria, partial agenesis of the corpus callosum, ventriculomegaly, vermian hypoplasia, and parenchymal calcifications.

affected infants. The primary target of the Zika virus is the neural progenitor cells, with immature neurons affected to a lesser extent. (2)

Symptoms such as fever, headache, arthralgia, myalgia, conjunctivitis, and maculopapular rash are suggestive of maternal infection with Zika virus. Risk of birth defects is highest if the infection is reported in the first trimester of pregnancy. (3)(4) Studies conducted in newborns with microcephaly due to Zika infection revealed a characteristic neuroimaging pattern that is distinct from other TORCH infections. (5) Fetal brain disruption sequence (severe microcephaly, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, and neurologic impairment), and brain anomalies (subcortical intracranial calcifications, severe cortical malformations, ventriculomegaly, agenesis of the corpus callosum, severe damage to the cerebellum, brain stem, and thalami), are characteristic and highly suggestive of congenital Zika virus infection. (2)(6) Ocular abnormalities associated with this entity include cataracts, coloboma, chorioretinal atrophy, focal pigment mottling of the retina, optic nerve hypoplasia, and atrophy. (2)(5) Extracranial abnormalities in congenital Zika virus syndrome include talipes, arthrogryposis, hyperflexion of the fingers, and diaphragm palsy. (2)(7)

Prenatal ultrasonography performed in the first trimester and early part of the second trimester (before 21 weeks' gestation) often yields false-negative results by detecting no abnormalities. (4) In addition, current laboratory testing for Zika virus has its limitations. Because of the delayed development, subsequent waning of Zika virus IgM, and the transient presence of the viral RNA in pregnancy, these tests may have negative results. (6) Physicians should be aware of Zika virus endemic regions and consider evaluating for congenital Zika virus infection in infants who have clinical signs suggestive of congenital Zika virus syndrome. Maternal risk factors such as travel history to endemic areas or sexual contact with a person who traveled to such an area should be considered. Also at high risk are infants whose mothers have laboratory evidence suggestive of Zika virus infection during pregnancy. (6)

Postnatal Management

Congenital Zika virus infection is multisystemic. Multidisciplinary management includes neurology, ophthalmology, otolaryngology, orthopedic surgery, cardiology, endocrinology, genetics, and infectious diseases as indicated. Upon discharge, close supervision by a pediatrician and multidisciplinary follow-up is essential. (6)

Lessons for the Clinician

- A normal first- and second-trimester ultrasonography scan is not necessarily reassuring in cases of suspected congenital Zika virus infection. Adequate investigations and follow-up are essential in mothers at high risk for Zika infection.
- In the absence of maternal use of teratogens and negative laboratory results for other congenital infections, specific neuroimaging findings described herein are highly suggestive of congenital Zika virus syndrome.
- Zika virus syndrome should be considered in the differential diagnosis of an infant with microcephaly and multiple brain malformations.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effects on the fetus and/or newborn infant of other maternal infections (eg, malaria) and their management.
- Know the causes, diagnosis, management, and outcome of an infant with microcephaly.

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ANSWER KEY FOR OCTOBER 2018 NEOREVIEWS

Diagnosing and Managing Hirschsprung Disease in the Newborn: 1. D; 2. E; 3. C; 4. B; 5. B.

Radiologic Approach to the Diagnosis of Bowel Emergencies in Neonates: 1. B; 2. E; 3. A; 4. B; 5. C.

Term Oligohydramnios and Prolonged Decelerations

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal values for arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min

AUTHOR DISCLOSURE Drs Demasio and Kuba have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. **Arterial Umbilical Cord Gas Values**

	pH	Pco_2 (mm Hg)	Po_2 (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤−10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤−10
Metabolic acidosis	<7.20	<60	Variable	≥−10
Mixed acidosis	<7.20	>60	Variable	≥−10

*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695.

- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable
Minimal: Amplitude range is greater than undetectable to 5 beats/min
Moderate: Amplitude range is 6–25 beats/min
Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes

  – Normal: ≤5 contractions in 10 minutes
  – Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:

  – Baseline rate: 110 to 160 beats/min
  – Baseline FHR variability: Moderate

  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - ■ Recurrent late decelerations
    - ■ Recurrent variable decelerations
    - ■ Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol*. 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum FHR monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

History

A 27-year-old gravida 2, para 0-0-1-0 woman was referred to the Maternal-Fetal Assessment Center at 40 4/7 weeks' gestation for postdate antenatal testing. At the time of her assessment, her blood pressure was newly elevated to 140/75 mm Hg, and oligohydramnios was diagnosed. Ultrasonography revealed an amniotic fluid index (AFI) of 5 cm and maximum vertical pocket of 1.9 cm, indicating the absence of a 2×2–cm amniotic fluid pocket. The nonstress test was reactive but demonstrated a spontaneous deceleration (Fig 1). Given these findings in a postdate gestation, she was referred to the labor and delivery (L&D) department with a recommendation for induction of labor.

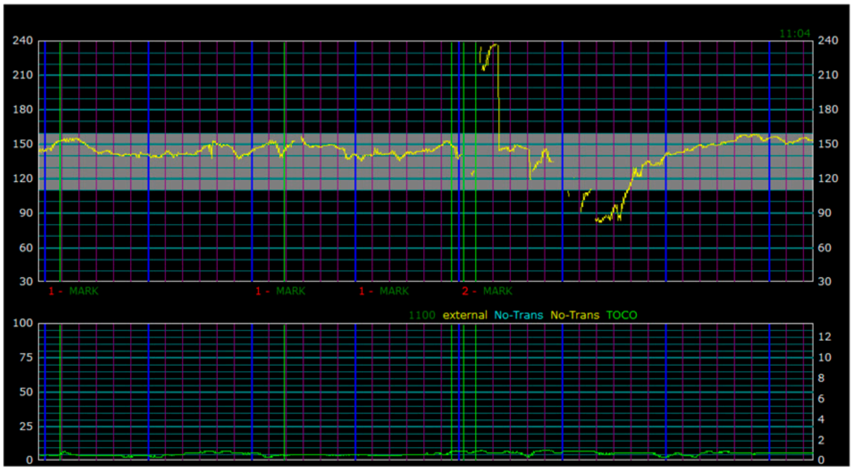

Figure 1. Electronic fetal monitoring strip 1.

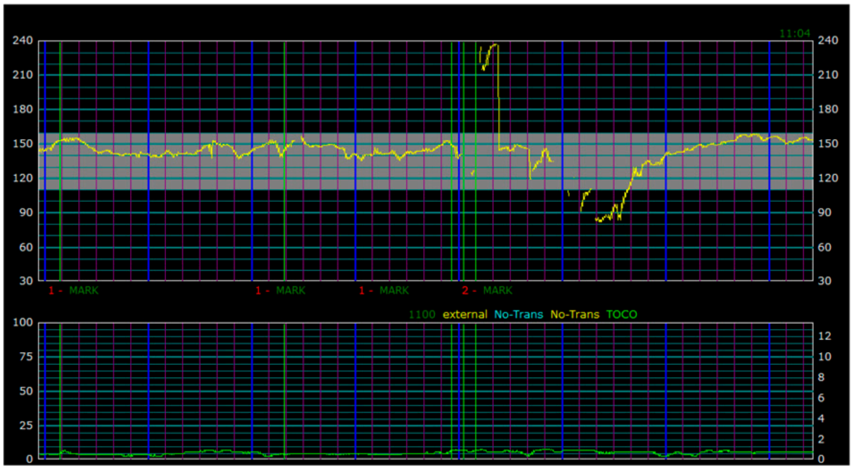

Figure 1. Electronic fetal monitoring strip 1.

Findings on EFM strip 1 were as follows:

- Baseline rate: 140 beats/min
- Baseline variability: Moderate
- Episodic patterns: Variable deceleration to nadir of 80 beats/min
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Reassuring FHR tracing with a variable deceleration

Case Progression

The woman's medical history was significant for polycystic ovarian syndrome and class 3 obesity. Her prenatal course was otherwise uncomplicated. The pregnancy dating was based on her last menstrual period, which was consistent with ultrasonography findings at 10 weeks' gestation. Her only medication was prenatal vitamins. She had 15 prenatal visits, and all laboratory values were within normal limits, including a glucose challenge test at 25 weeks' gestation. Her third-trimester group B *Streptococcus* culture was negative, but was obtained more than 4 weeks before her admission to L&D.

Upon arrival at L&D, an initial examination revealed a blood pressure of 140/76 mm Hg, pulse of 104 beats/min, normal temperature, and a body mass index of 41.7 kg/m^2. She had no complaints and denied any symptoms of pre-eclampsia. Her cervix was found to be 1-cm dilated, with 20% effacement, and the vertex was at −3 station. The estimated fetal weight (EFW) was assessed using Leopold maneuvers to be 3,500 g, which was consistent with her third-trimester ultrasonography findings at 31 weeks' gestation, which indicated an EFW of 1,520 g. Her pelvis was felt to be adequate for vaginal delivery. Admission laboratory values were within normal limits and did not show any evidence of pre-eclampsia. The FHR tracing was initially category 1, but because of a prolonged 2-minute deceleration (Fig 2), induction was started with a transcervical Foley balloon catheter and simultaneous use of oxytocin. The FHR tracing before and after the deceleration had moderate variability and accelerations, and was felt to be reassuring.

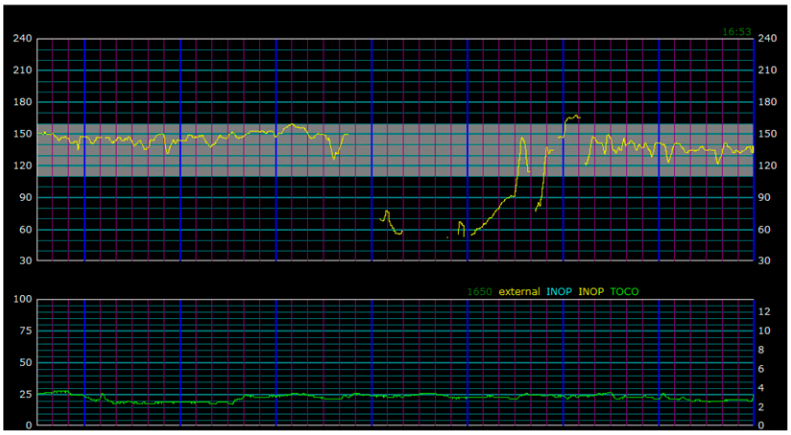

Figure 2. Electronic fetal monitoring strip 2.

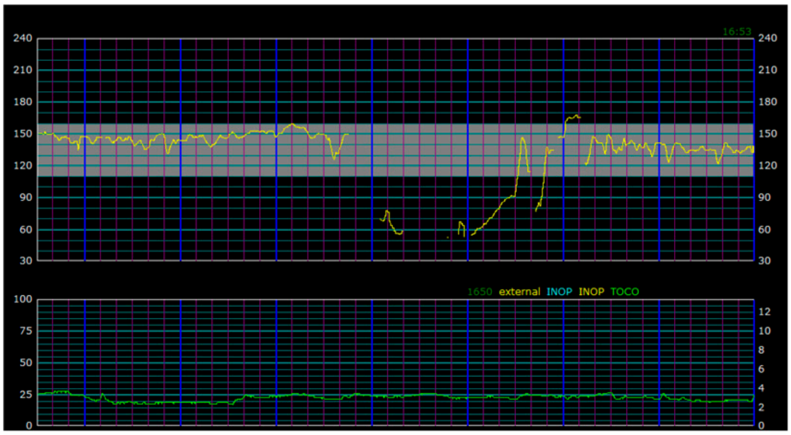

Figure 2. Electronic fetal monitoring strip 2.

Findings on EFM strip 2 were as follows:

- Baseline rate: 140 beats/min
- Baseline variability: Moderate
- Episodic patterns: Prolonged deceleration
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Cord compression or placental insufficiency

Two hours after initiating labor induction, epidural analgesia was administered and the FHR tracing showed episodic repetitive shallow decelerations characteristic of late decelerations. The absence of contractions, however, limited the interpretation of the FHR pattern (Fig 3).

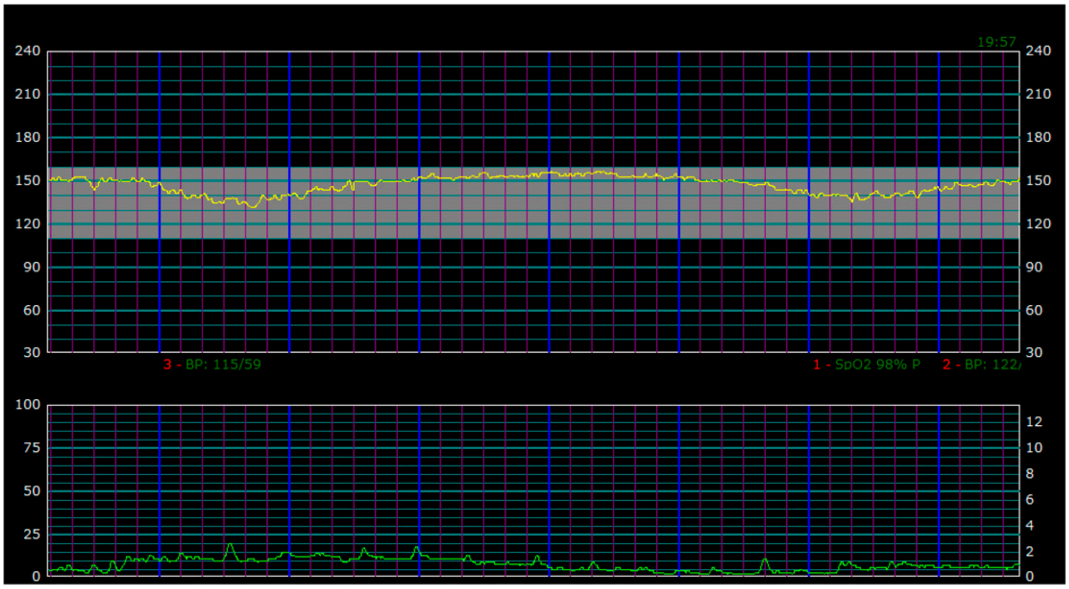

Figure 3. Electronic fetal monitoring strip 3.

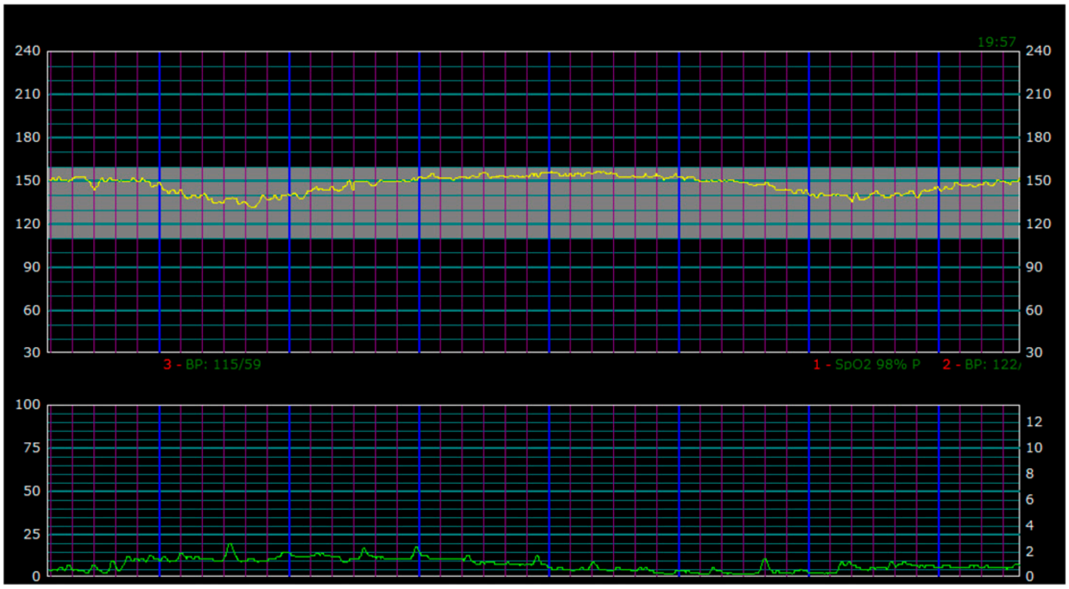

Figure 3. Electronic fetal monitoring strip 3.

Findings on EFM strip 3 were as follows:

- Baseline rate: 150 beats/min
- Baseline variability: Minimal
- Episodic patterns: Recurrent decelerations
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Late decelerations, acidosis, nonreassuring tracing

Maternal blood pressure at this time decreased to 105/58 mm Hg, and vaginal examination revealed that the cervical Foley balloon catheter had been expelled. The cervix was now 5-cm dilated, 50% effaced, and at −3 station. Oxytocin infusion was stopped to allow for intrauterine resuscitation and maternal repositioning. The FHR tracing soon returned to moderate variability, but after continued inability to view contractions, membranes were artificially ruptured and an intrauterine pressure catheter (IUPC) was placed. Clear amniotic fluid was presumed, and by this point in the labor process, she was given a diagnosis of gestational hypertension due to persistent blood pressure elevations. Because the FHR tracing was reassuring, and an IUPC was in place, oxytocin infusion was restarted and the induction continued for 6 more hours until another 2-minute deceleration occurred. This deceleration was clearly associated with a contraction (Fig 4).

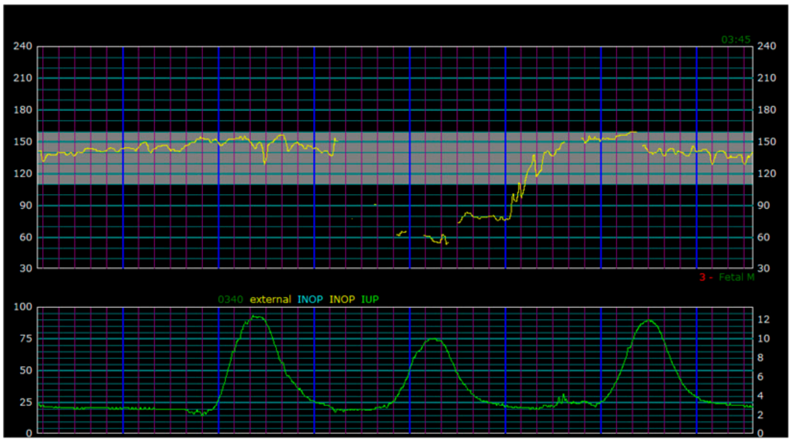

Figure 4. Electronic fetal monitoring strip 4.

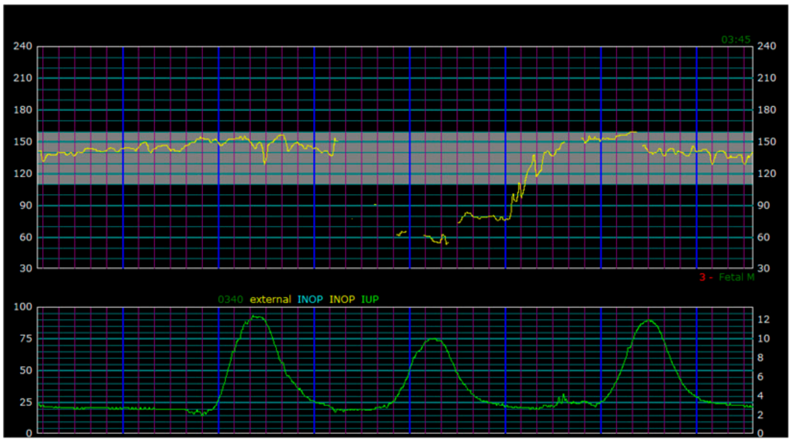

Figure 4. Electronic fetal monitoring strip 4.

Findings on EFM strip 4 were as follows:

- Baseline rate: 140 beats/min
- Baseline variability: Moderate
- Episodic patterns: None
- Periodic patterns: Prolonged deceleration
- Uterine contractions: Every 2 minutes
- Interpretation: Category II
- Differential diagnosis: Cord compression, abnormal cord location, placental insufficiency

The cervix was examined and initially thought to be 6-cm dilated, 70% effaced, and at −3 station; however, when another deceleration occurred 4 hours later (Fig 5), she was reexamined by another clinician who thought the cervix was less dilated at 4 cm, with 70% effacement, and at −3 station.

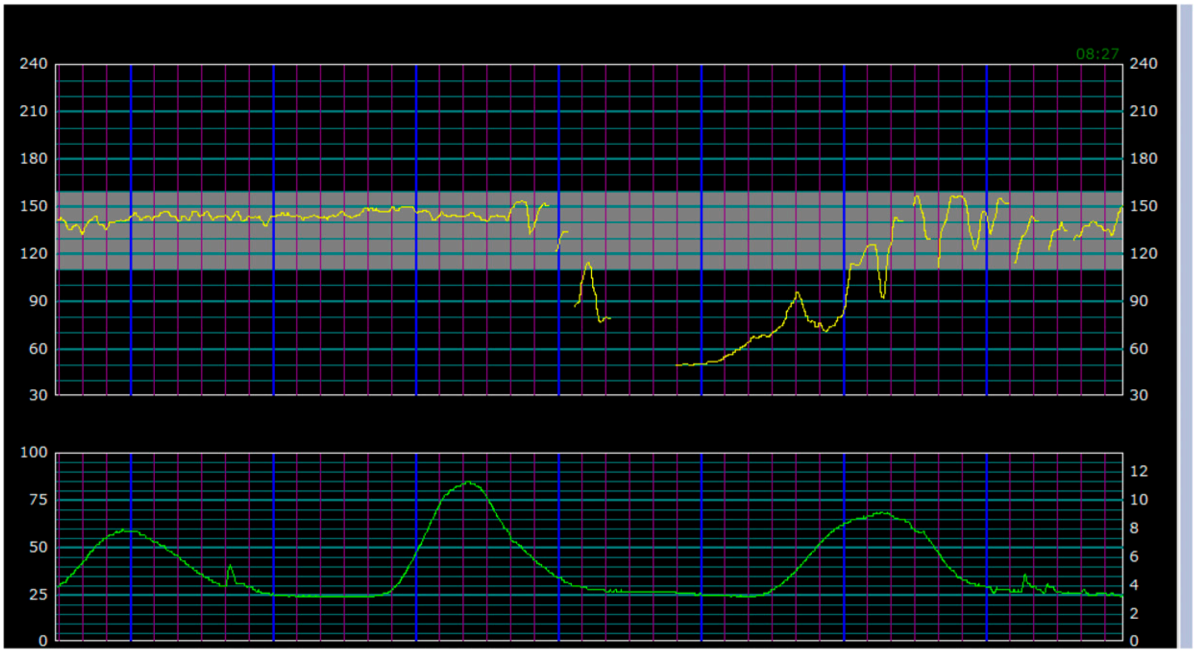

Figure 5. Electronic fetal monitoring strip 5.

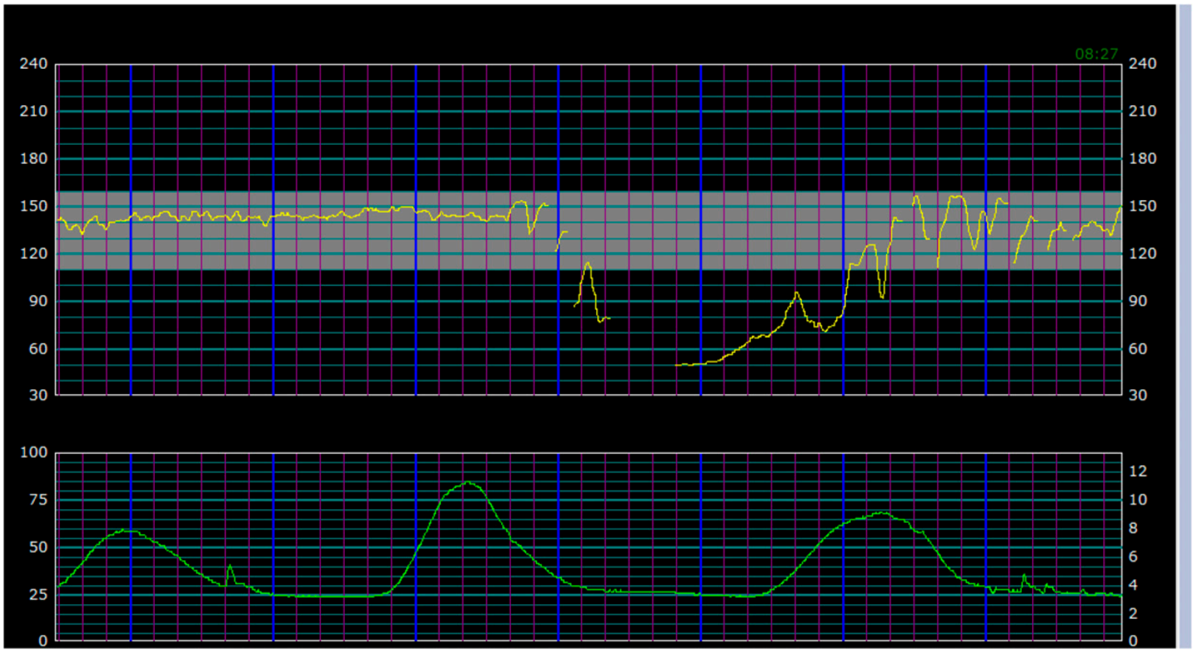

Figure 5. Electronic fetal monitoring strip 5.

Findings on EFM strip 5 were as follows:

- Baseline rate: 140 beats/min
- Baseline variability: Minimal
- Episodic patterns: None
- Periodic patterns: Prolonged deceleration with loss of variability within the deceleration
- Uterine contractions: Every 2 to 3 minutes
- Interpretation: Category II
- Differential diagnosis: Worsening fetal status, fetal intolerance of labor

Shortly thereafter, the FHR tracing progressed to recurrent late decelerations, maintaining moderate variability (Fig 6) and oxytocin infusion was held again.

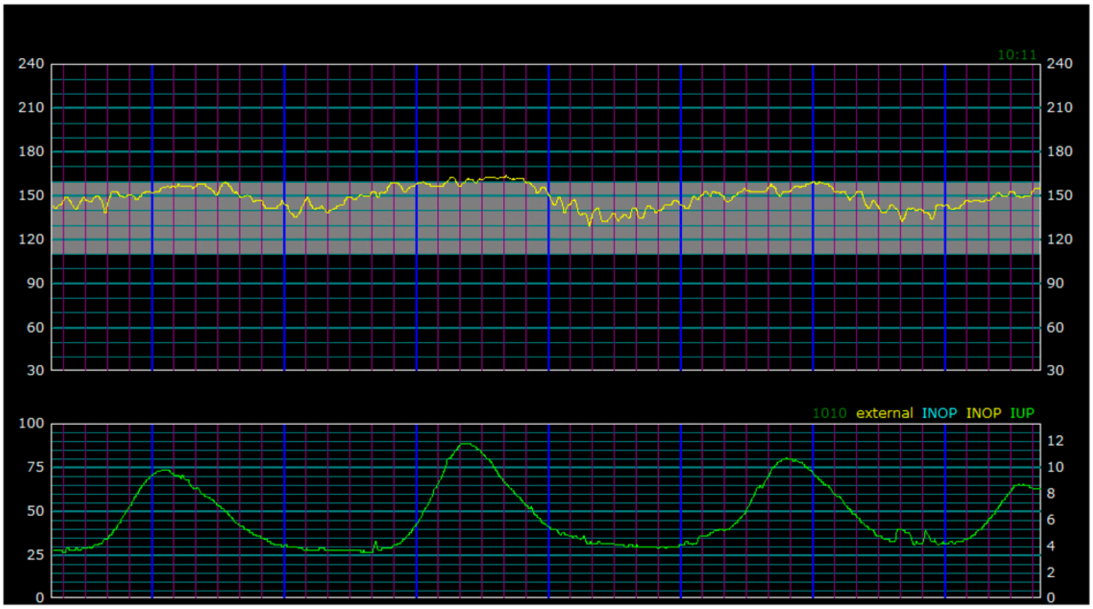

Figure 6. Electronic fetal monitoring strip 6.

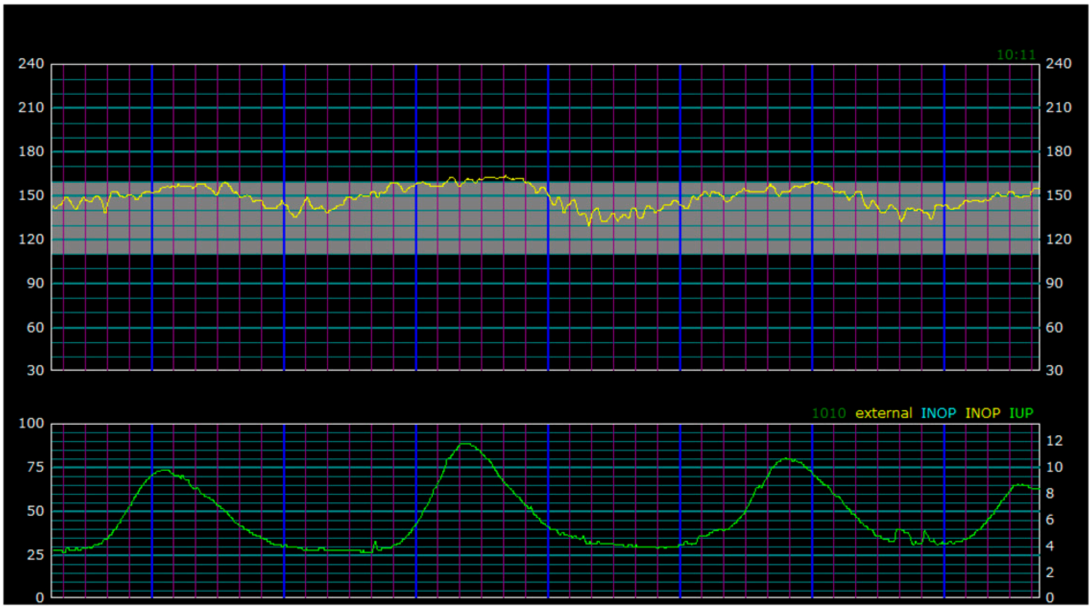

Figure 6. Electronic fetal monitoring strip 6.

Findings on EFM strip 6 were as follows:

- Baseline rate: 150 beats/min
- Baseline variability: Moderate
- Episodic patterns: None
- Periodic patterns: Recurrent late decelerations
- Uterine contractions: Every 2 to 3 minutes
- Interpretation: Category II
- Differential diagnosis: Non-reassuring fetal status

The FHR tracing progressed to tachycardia with minimal variability (Fig 7).

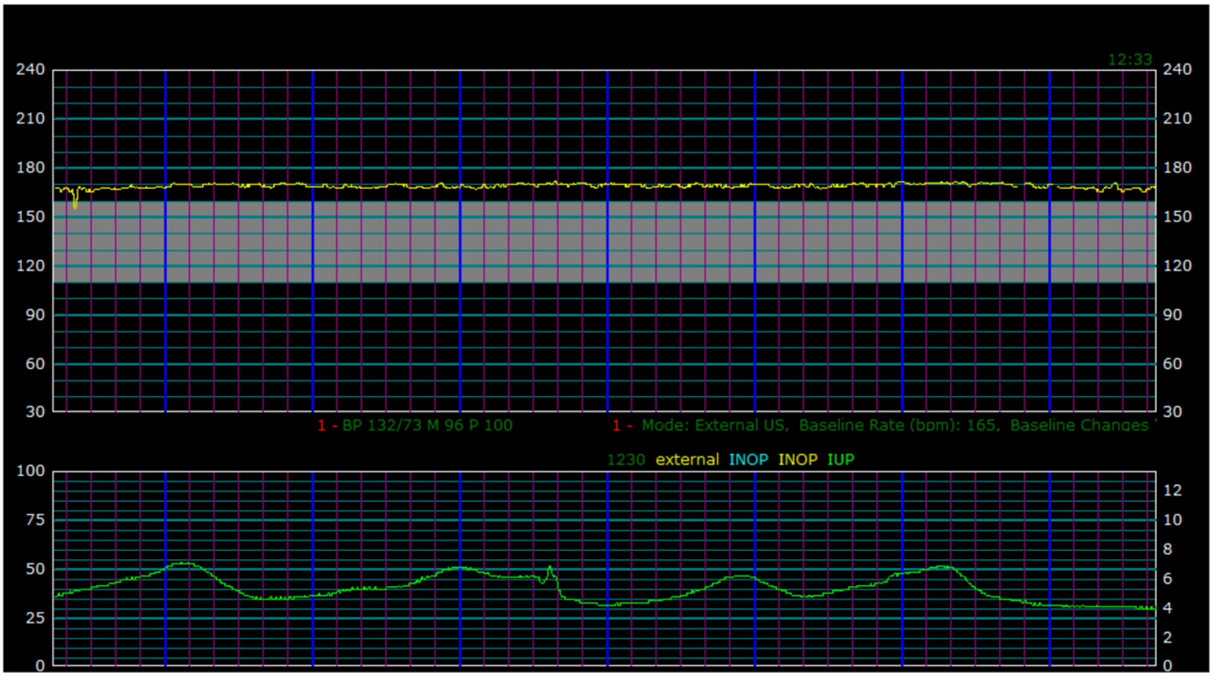

Figure 7. Electronic fetal monitoring strip 7.

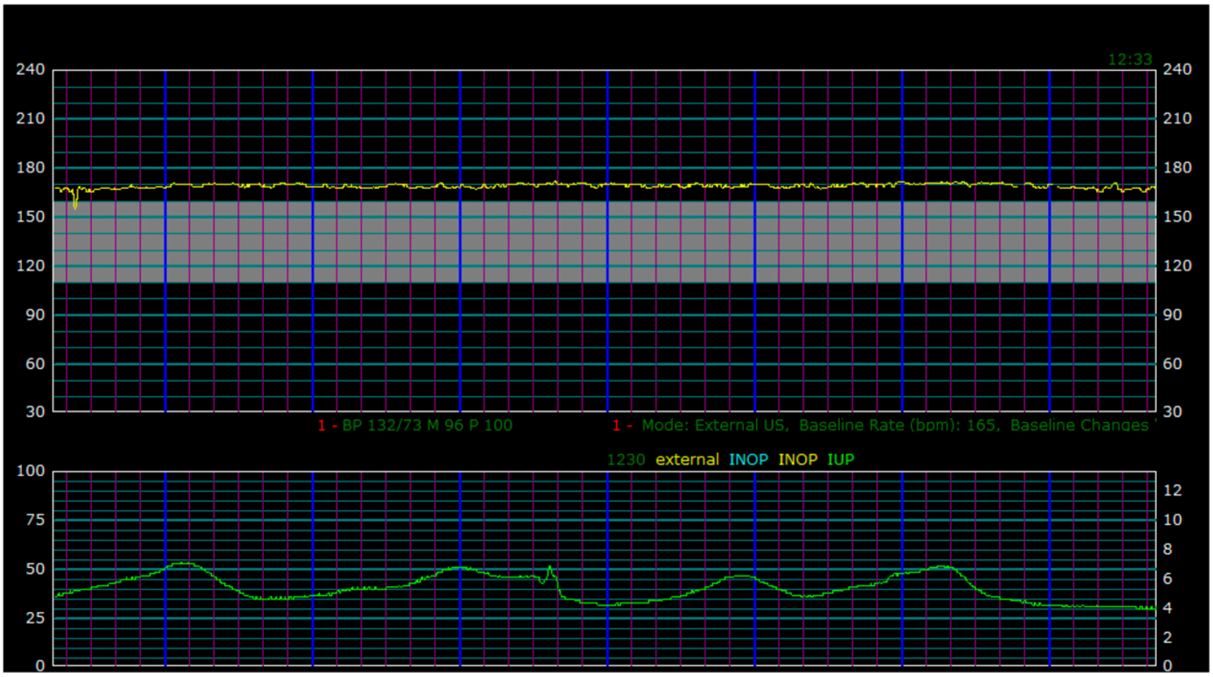
12:33
240
210
180
150
120
90
60
30
1 - BP 132/73 M 96 P 100
1 - Mode: External US, Baseline Rate (bpm): 165, Baseline Changes
1230 external INOP INOP IUP
100
75
50
25
0
12
10
8
6
4
2
0

Figure 7. Electronic fetal monitoring strip 7.

Findings on EFM strip 7 were as follows:

- Baseline rate: 170 beats/min
- Baseline variability: Minimal
- Episodic patterns: None
- Periodic patterns: Tachycardia
- Uterine contractions: Every 1 to 2 minutes
- Interpretation: Category II
- Differential diagnosis: Worsening fetal status, maternal intrapartum fever

Fetal scalp stimulation elicited an acceleration that was thought to be reassuring for a nonacidotic fetus (Fig 8).

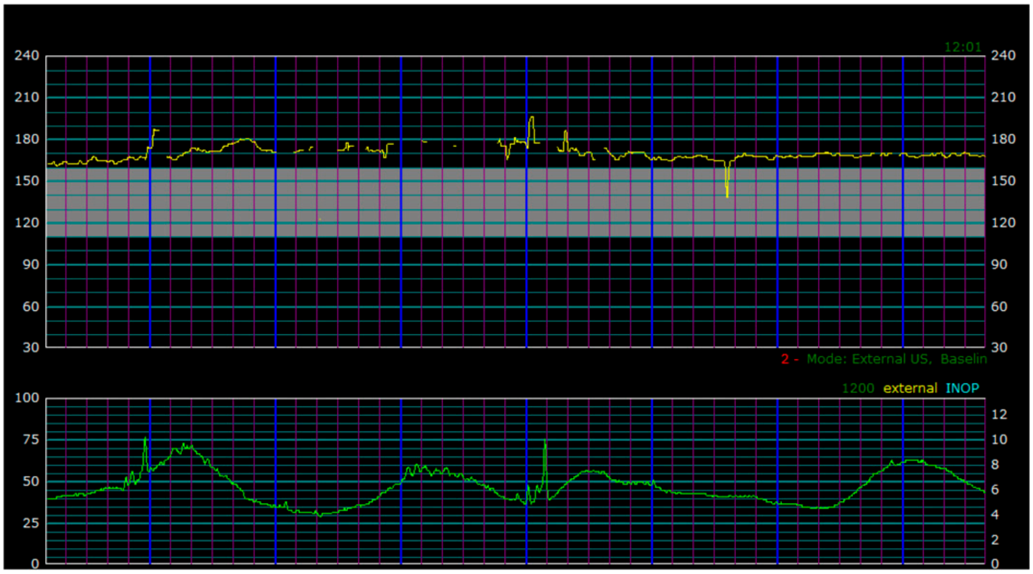

Figure 8. Electronic fetal monitoring strip 8.

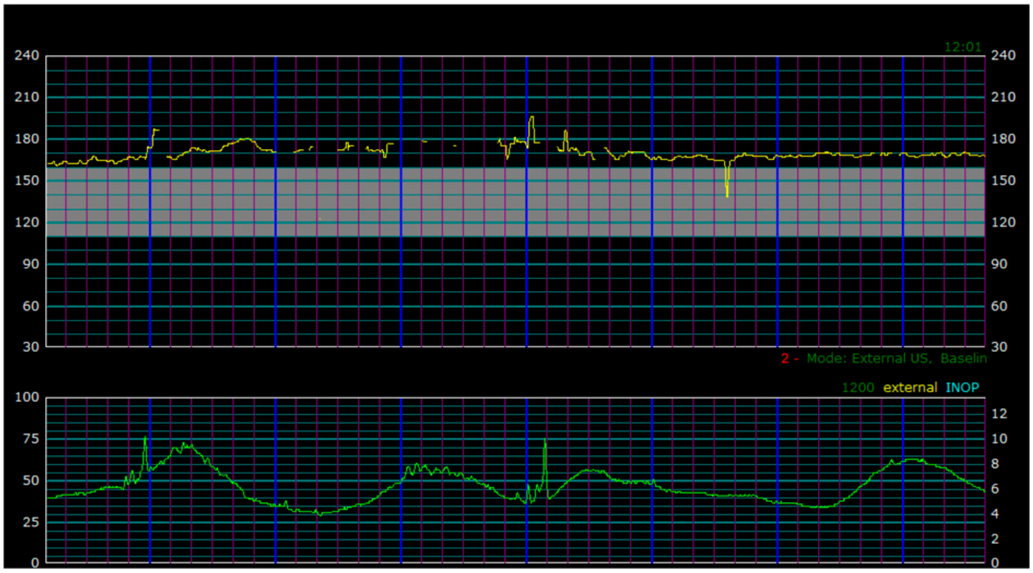

Figure 8. Electronic fetal monitoring strip 8.

Findings on EFM strip 8 were as follows:

- Baseline rate: 170 beats/min
- Baseline variability: Minimal
- Episodic patterns: None
- Periodic patterns: Tachycardia with possible acceleration at the time of scalp stimulation
- Uterine contractions: 1 to 3 minutes
- Interpretation: Category II
- Differential diagnosis: Possibly reassuring fetal status, maternal fever, worsening acidosis

At this point, approximately 15 hours after the start of labor induction for oligohydramnios, a cesarean delivery was recommended by the clinician, with the acknowledgment that the fetus was unable to tolerate the induction process, and the patient was remote from a vaginal delivery. In preparation for cesarean, the epidural catheter was infused with medication by the anesthesiologist to achieve adequate anesthetic levels. The patient suddenly became pale and diaphoretic, and complained of shortness of breath. The FHR decelerated into bradycardia in the presence of tachysystole (Fig 9).

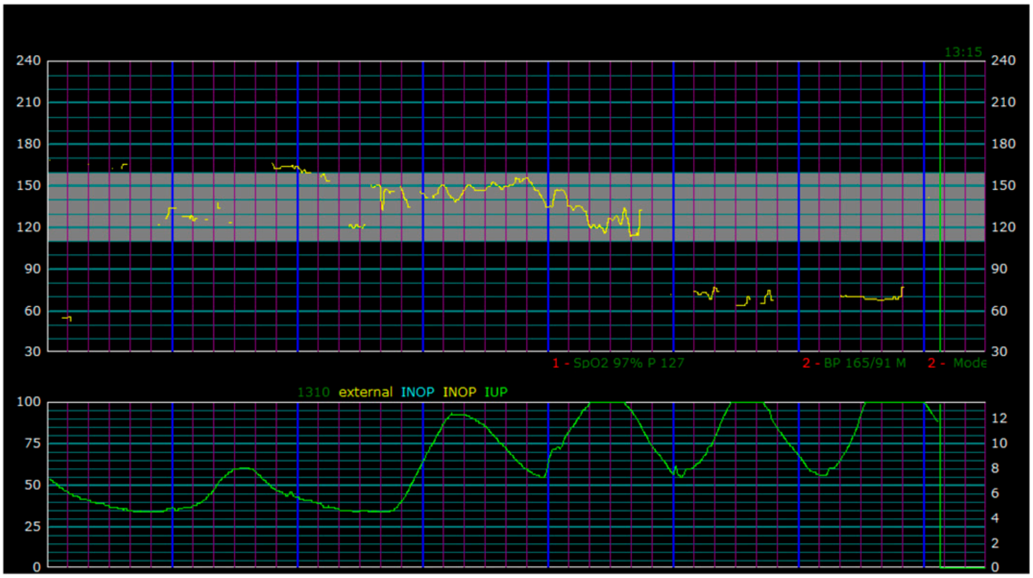

Figure 9. Electronic fetal monitoring strip 9.

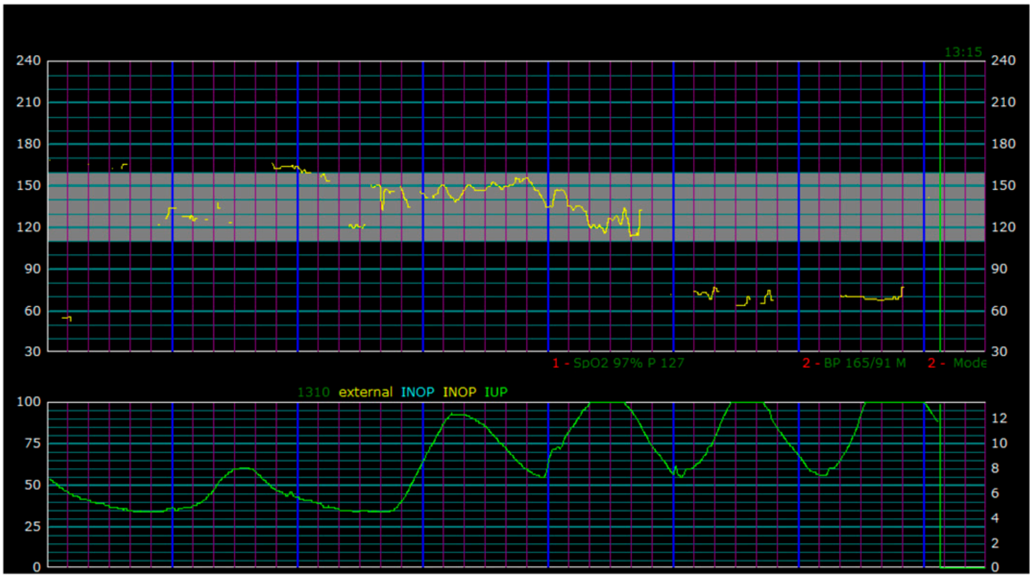

Figure 9. Electronic fetal monitoring strip 9.

Findings on EFM strip 9 were as follows:

- Baseline rate: Indeterminate
- Baseline variability: Moderate
- Episodic patterns: None
- Periodic patterns: Prolonged deceleration, preterminal bradycardia
- Uterine contractions: 1 minute, tachysystole
- Interpretation: Category III
- Differential diagnosis: Non reassuring fetal status, secondary fetal response to maternal sympathectomy from epidural, acidosis

The clinicians proceeded with expeditious cesarean. At the time of delivery, the amniotic fluid was stained with thick meconium. The surgery was complicated by uterine atony that was treated with the administration of uterotonics and placement of compression sutures. After surgery, the patient did well, and was discharged on postoperative day 4.

A viable female infant was delivered 10 minutes after the onset of bradycardia and was immediately evaluated and provided resuscitation by the pediatricians in attendance at the cesarean delivery. The infant's birthweight was 2,545 g (1%), which was 1,000 g less than estimated. The umbilical cord gases are shown in Table 2. The infant was initially limp without respiratory effort, requiring positive pressure ventilation and eventually continuous positive airway pressure. The 1-, 5-, and 10-minute Apgar scores were 3, 6, and 7, respectively. The neonate was admitted to the NICU where her course was further complicated by pneumothorax, gram-negative sepsis, and hypoglycemia. She was treated with antibiotics, weaned to room air, and ultimately discharged on day of life 21.

DISCUSSION

Induction of labor for uncomplicated pregnancies with isolated oligohydramnios between 40 and 41 6/7 weeks' gestation is a commonly used management strategy with limited evidence to support its benefit. The rationale for this intervention is to prevent a term stillbirth. A single randomized trial on this subject was reported in which 54 women were randomized to either expectant management or induction of labor. The trial found no difference in perinatal outcomes, mode of delivery, or stillbirth for women who received expectant management or had labor

TABLE 2. **Umbilical Cord Gases**

	pH	Pco_2 (mm Hg)	PO_2 (mm Hg)	BASE EXCESS (mEq/L)
Arterial	6.93	114	30.9	–8.5
Venous	6.98	111	17	–5.6

induction. (1) Another investigation of 3,049 women within the same gestational age range found that 11% of the pregnancies had an AFI less than 5, and of these pregnancies, 35% had a higher rate of cesareans for nonreassuring FHR tracing (relative risk [RR]=2.1, 95% confidence interval [CI]=1.4–3.2) and small-for–gestational age neonates (RR=2.3; 95% CI=1.7–3.2). (2) In addition, a meta-analysis of 12 trials that included approximately 36,000 women with term oligohydramnios also reported an increase in NICU admissions and low Apgar scores along with an increased rate of cesarean deliveries. (3) The difference in the outcomes reported may be due to associated clinical factors.

When faced with term oligohydramnios in a seemingly uncomplicated pregnancy, the challenge of interpreting FHR decelerations that occur include accounting for all other clinical factors. This case demonstrates that although the pregnancy was well dated, and a third trimester ultrasound examination was performed, the EFW did not reflect the small-for–gestational age neonate that was ultimately delivered. This signifies the limitation of third trimester ultrasound examinations performed in obese women. Maternal obesity in this case also restricted use of the external fetal monitor to correctly detect contractions. Oligohydramnios in this term gestation was associated with prolonged decelerations throughout the first stage of labor, increasing the risk for a poor outcome.

A prolonged deceleration, based on the NICHD definition, refers to an "apparent decrease in FHR below the baseline…the decrease in the FHR is 15 bpm or more and lasts at least 2 minutes but less than 10 minutes from onset to return to baseline." (4) Other than this description of a prolonged deceleration, there are few if any clinical studies that reflect the neonatal outcomes of fetuses that exhibit prolonged decelerations during antenatal testing or in the intrapartum period. This type of pattern is usually attributed to umbilical cord compression resulting from contractions, abnormal cord location, or placental insufficiency. In the setting of oligohydramnios, all 3 causes are plausible. Contraction forces decrease blood flow to the fetus and limit the time for adequate gas exchange at the level of the maternal-placental interface. The risk of fetal acidemia is dependent on the duration of the insult as well as the reserve of the fetus.

In the clinical setting of prolonged decelerations with oligohydramnios that accompanies a slowly progressing labor, such as found with induced labor, it is imperative to recognize a fetus that may have decreasing reserve, as reflected in an FHR tracing that is progressing toward a state of acidemia. Longitudinal assessment of the FHR tracing is required to recognize a category 1 tracing that is deteriorating to category III. The sequence of progressive FHR tracing deterioration has been described. (5) First, there is a loss of accelerations as moderate baseline variability is preserved. Significant decelerations develop, such as prolonged decelerations, and frequent episodes of tachycardia, or baseline tachycardia associated with minimal variability develops. Absent variability during decelerations are seen, and ultimately preterminal bradycardia occurs. (5)

In this case, the decision to perform a cesarean due to fetal intolerance of labor was appropriate; however, the fetus was unable to tolerate the epidural load that caused maternal symptoms of shortness of breath, and likely decreased maternal afterload, further compromising uterine perfusion. This last stressor led to an emergent delivery of a fetus with little intrauterine reserve.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the significance of oligohydramnios and the management of pregnancy when it is diagnosed.

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Newborn with Neck Lesion

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**Division of Neonatology, Department of Pediatrics, East Carolina University/Vidant Medical Center, Greenville, NC*

THE CASE

A 2-day-old term male infant presents with a lesion located on the ventral surface of the neck.

Prenatal and Birth Histories

- Male neonate was born at 38 weeks' gestational age to a 29-year-old, gravida 3 para 2 white woman who had an uncomplicated pregnancy.
- History of human papillomavirus, diagnosed in the third trimester of pregnancy.
- Maternal laboratory findings were unremarkable.
- The infant was delivered via spontaneous vaginal delivery. No resuscitation was required.
- Apgar scores were 8 at 1 minute and 9 at 5 minutes.
- Birthweight was 3,550 g.

Presentation

The infant developed respiratory distress at 2 hours of age with tachypnea and retractions. He was initially treated with continuous positive airway pressure (CPAP) and heated humidified high-flow nasal cannula. He was noted to have a lesion located on the ventral surface of the neck. He was transported to our facility at 2 days of age for further management.

Vital signs included the following.

- Temperature: 99.1°F (37.3°C)
- Heart rate: 158 beats/min
- Respiratory rate: 84 breaths/min
- Blood pressure: 70/21 mm Hg (mean arterial pressure, 38 mm Hg)
- Oxygen saturation: 96% on CPAP +6 mm Hg with a fraction of inspired oxygen of 0.6

Physical Examination

- Head, ears, eyes, nose, and throat examination: Fontanels soft and flat, sutures approximated, nares patent. Lesion noted on the ventral area of the neck. Lesion consisted of a 0.5-cm skin projection at the upper end and a sinus or fistulous tract at the lower end of the lesion (Figs 1 and 2). No surrounding erythema. No discharge.
- Chest: Tachypnea and grunting on CPAP.
- Cardiovascular: Normal heart sounds S1 and S2 with no murmurs. Pulses normal and equal in all extremities, capillary refill normal, skin perfusion normal.
- Abdomen: Soft and not distended.
- Genitourinary: External genitalia normal, testes descended.

AUTHOR DISCLOSURE Drs Aboaziza and Akpan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

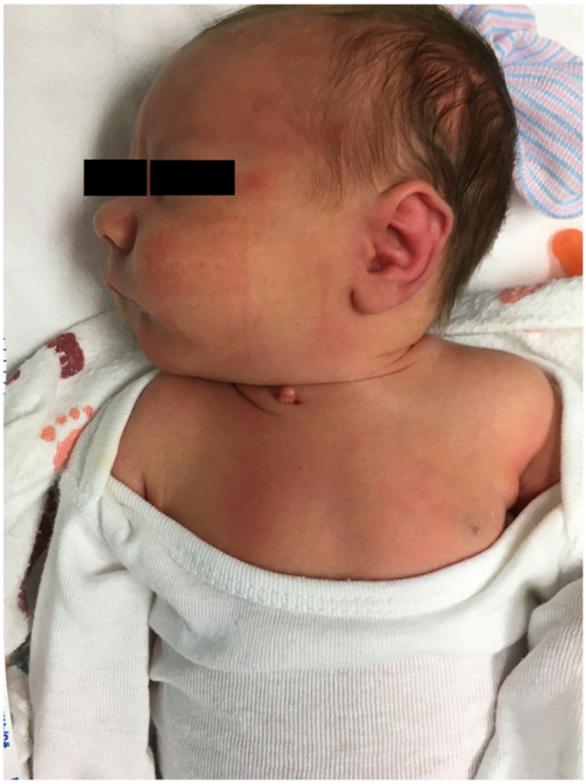

Figure 1. Newborn with midline neck lesion at 8 days after birth.

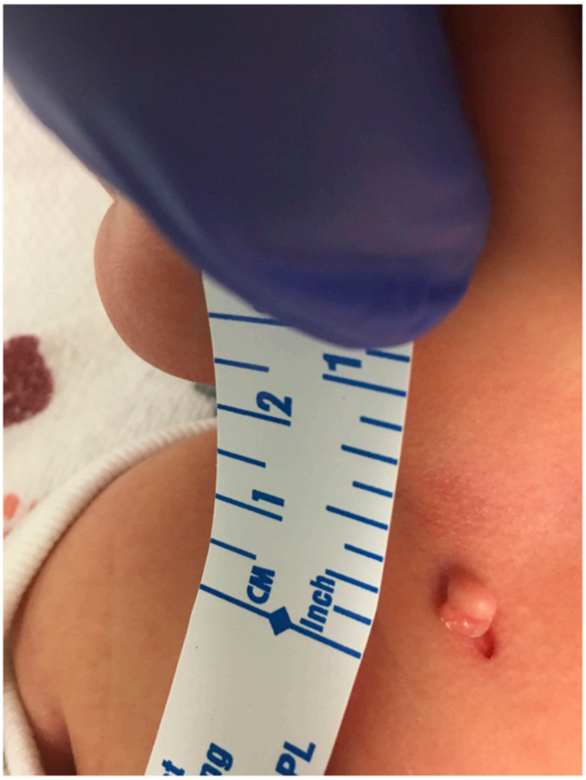

Figure 2. Newborn with midline neck lesion at 8 days after birth (close-up).

- Musculoskeletal: Muscle mass normal.
- Skin: Intact and appropriate for gestational age.
- Spine/back: No anomalies observed or palpated.
- Neurologic: Tone appropriate for gestational age.

Laboratory Studies

- Complete blood cell count: Normal.
- Basic metabolic panel: Normal.
- Blood culture: Negative.
- Total bilirubin level: 12.5 mg/dL (213 μmol/L) at 47 hours of age. Infant's blood type: O+, Coombs negative.

Imaging Studies

- Chest radiography: Ground glass appearance with low lung volumes; normal skeletal findings.

Progression

Surfactant was administered endotracheally using the INtubation SURFactant Extubation (INSURE) technique. Respiratory support was gradually weaned and discontinued at 6 days of age. Empiric antibiotics were discontinued after 48 hours because blood cultures were documented as being sterile. The infant's indirect hyperbilirubinemia was treated with phototherapy. Enteral feedings were initiated at 3 days of age. The infant tolerated ad lib breastfeedings with adequate weight gain. The pediatric surgery team was consulted to assess the neck lesion and made a presumptive diagnosis. The team recommended outpatient follow-up with a plan for surgery at a later date. The infant was discharged from the hospital with a 1-month outpatient follow-up scheduled with pediatric surgery.

DIFFERENTIAL DIAGNOSIS

- Thyroglossal duct cyst
- Congenital midline cervical cleft
- Branchial cleft anomaly
- Pyriform sinus fistulae
- Bronchogenic cyst
- Dermoid cyst

ACTUAL DIAGNOSIS

Congenital midline cervical cleft

What the Experts Say

Congenital midline cervical cleft (CMCC) is a rare anomaly located on the ventral surface of the neck and may present at any level between the mandible and the manubrium of the sternum. It was documented in the literature as early as 1848 by Luschka, a German anatomist. (1) The incidence is ~2% among all congenital cervical malformations. (2)

The exact cause is unknown but CMCC is thought to be the result of impaired fusion of the distal branchial arches in the midline. (3) It is typically an isolated anomaly, previously reported as occurring predominantly in white female babies (4) but case reports increasingly appear to show a more even distribution among the sexes.

Diagnosis of CMCC is made primarily on physical examination. Although rare, with fewer than 200 published cases to date, the presentation is typical, and rapid and accurate diagnosis is possible on physical examination. (2) It presents as a nipplelike skin tag superiorly and a thin vertical band with a blind-ending sinus tract caudally. (4)(5) At birth, the external layer of the cleft may consist of an erythematous weeping membrane that becomes atrophic, leading to scarring and a resultant fibrous cord as the patient grows. Cervical contracture could lead to restriction of neck extension, micrognathia, or torticollis in early childhood. (4) Ultrasonography may be warranted to examine the surrounding neck structures to rule out associated anomalies. (6) Associated anomalies may include thyroglossal duct cyst and clefts of the mandible, tongue, or lower lip. (6)(7) CMCC is treated with surgical excision of skin, fibrous cord, and caudal sinus, along with removal of an associated cyst, if present. (8) Complete surgical excision at an early age is preferable because it leads to better results with less retractile scarring and prevention of cervical contractures. (7)(8)

Because CMCC has a typical presentation, the other possible diagnoses could be rapidly excluded. Thyroglossal duct cysts are the most common congenital neck lesions. They may be midline but usually present as masses without a sinus tract or nipplelike appearance, and have no discharge. Branchial cleft anomalies present as cysts, sinuses, or fistulae but they are typically located in the lateral neck. Affected infants present with a mass, skin pit, or drainage from the site of the lesion. Pyriform sinus fistulae are rare, and are also usually located in the lateral neck, more commonly the left side. Bronchogenic cysts and dermoid cysts are uncommonly located in the cervical region and typically present as masses without a sinus. The distinction may be made with imaging studies but definitive diagnosis is made on histopathologic examination—respiratory epithelium is found in bronchogenic cysts, and complex tissues such as hair, sweat glands, skin, and bone are found in dermoid cysts.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical manifestations of branchial cleft cysts.
- Know the clinical manifestations and approaches to therapy of neck masses in the newborn infant.

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Answer Key appears on page e711.

Beyond the First Breath: Hyaline Membrane Disease and Constructing the Neonatal Patient, 1959–1975

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Mary Ellen Avery, MD. Photograph kindly provided by Rosalind S. Brown, MD.

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ABBREVIATIONS

HMD	hyaline membrane disease
NIH	National Institutes of Health
UCLA	University of California, Los Angeles

INTRODUCTION

How do the lungs of newborns support their first breaths, and why do some infants develop respiratory distress? This crucial research question emerged in the 1950s and was investigated by numerous physicians and scientists, including the American pediatrician Mary Ellen Avery, who devoted her career to the regulation of infant respiration. In a 1964 lecture, Avery drew a distinction between the intrauterine and extrauterine environments stating that "It is clearly at birth that regular rhythmic respiration begins. Something is turned on, something must be different just after birth from the way it was before, and this something must be essential to the regulation of respiration."(1)

Although Avery was a physician by training and not a scientist, research played a significant role in her career and led to her prominence as one of the investigational leaders of respiratory distress syndrome, which was known as hyaline membrane disease (HMD) during the time of Avery's research. Avery focused on the role of surfactant, specifically its deficiency in HMD, challenging the accepted view at the time that HMD was caused by an obstruction in the lungs due to the aspiration of hyaline membranes. (2)(3)(4) Avery's act of shifting the understanding of HMD from an obstructive disease to one of a biochemical deficiency was all the more striking given her role as a pediatrician and not a formally trained laboratory scientist. Biographers have estimated that her findings on HMD and their subsequent translation to treatment in the form of surfactant replacement have saved the lives of more than 800,000 infants. (2)

The discovery of surfactant deficiency as the cause of HMD in 1959 not only challenged the accepted understanding of the disease at the time, but it also redefined the relationship among multiple medical specialties, including pediatrics, obstetrics, and physiology, as they pertained to the premature infant population. In addition, the research initiative surrounding HMD lay the groundwork for the development of neonatology as a new medical specialty that valued both the clinic and laboratory.

Through an investigation of Avery's lectures, correspondence, and published work on HMD, an excerpt from the author's dissertation (5) aims to show that Avery's research on the disease ushered in a new era of newborn medicine, one that was particularly focused on the premature infant. Through her collaborations with physiologists and her physical-chemical approach to a problem that had historically been tackled with a "clinicoanatomic" focus, Avery's research on HMD became the foundation on which the care of the neonatal patient was shaped during the 1960s and 1970s. (6) Moreover, by translating these concepts for clinicians, Avery created a practical role for herself as an "introducer" between fields during the early years of her career as a woman in medicine. The influence of Avery's research on HMD in the neonate culminated in the development of NICUs during this period, which were highly technical spaces in which physicians, physician-scientists, basic scientists, and other medical practitioners held a stake.

PEDIATRICS, OBSTETRICS, AND THE "NEWBORN PATIENT"

Leading up to the mid-20th century, both pediatricians and obstetricians focused on clinical care of the newborn. At the Johns Hopkins University School of Medicine and Harvard Medical School, prominent medical centers at which Avery would later train and work, the departments of pediatrics and obstetrics were each tactful in their engagement with research and the types of investigative methods associated with their specialties. The field of pediatrics was becoming increasingly responsible for newborns, a patient population whose care presented an urgency, given the high infant mortality rate in the late 19th-century United States (estimated at 15%-20% in the first year after birth). (7) The involvement of pediatricians in newborn care, as well as the biochemical and basic science expertise they were continually refining, led to the framing of the newborn as a distinct "patient" whose care was provided at children's hospitals through specialized technologies.

In 1910, premature birth was found to be the leading cause of infant mortality in the United States, leading to an urgency to investigate diseases in the premature infant. This contributed to a burgeoning infant welfare movement beginning in 1914 that was led by a group of obstetricians including John Whitridge Williams, who was the chief of obstetrics at Johns Hopkins. (7)(8) As the professional reputation of obstetrics was dwindling at this time, Williams put forth a concerted effort to legitimize his specialty by appealing to the necessity of skill in childbirth and placing value on the technical training of obstetricians. (6)(7) Williams was not only concerned with infant welfare as a means of promoting his professional ambitions for obstetrics in the early 20th century, he was also interested in the type of research being conducted on pregnancy. In 1919, Williams was elected chairman of the Johns Hopkins' Department of Obstetrics, which was the first of its kind in the country. He championed research in obstetrical and gynecological pathology while also encouraging "the use of other approaches and laboratory methods, especially physiology and chemistry."(8) The pathological studies being conducted by the gynecological-obstetrical staff at Johns Hopkins reflected the clinicoanatomical approach to research, in which observations and materials gathered in the clinic were correlated to anatomical findings. (6)(8) Williams encouraged exploration of the "biological and biochemical aspects of pregnancy," which he found were insufficiently investigated and thus stunting the advancement of obstetrical knowledge. (8) The Department of Obstetrics and Gynecology at Harvard Medical School practiced a similar, highly technical approach to obstetrical training during the 1910s and 1920s. (9)

Although Williams was unable to launch a physical-chemical approach in obstetrical research during the early 20th century, his pediatric colleagues at Johns Hopkins were able to find more success in their biochemical endeavors. In

1912, the first chair of the department of pediatrics, John Howland, arrived at Johns Hopkins and was credited with reforming pediatrics by "substituting bedside observation and conjecture" for the "study of disease through laboratory methods and experiments."(8) Biochemistry was thought to have flourished for the 15 years following Howland's appointment, a period in which he strengthened the relationship between this scientific discipline and pediatrics and changed the culture of Johns Hopkins' Department of Pediatrics. (8) Students and physicians who passed through Howland's department were almost always "drawn into [his] vortex of biochemical research."(8) The network of physicians moving between Johns Hopkins and Harvard Medical School in the early 20th century transferred and perpetuated the strong relationship between biochemistry and pediatrics, leading to a linkage of clinical practice and physical-chemical research methods that was unable to be attained in obstetrics.

While pediatricians were investigating the chemical mechanisms of disease in the early 20th century, they were also devoting increased attention to the clinical care of the newborn. A particularly notable development in the first half of the 20th century between pediatrics and the care of newborns was at the Sarah Morris Children's Hospital in Chicago, where the pediatrician Julian Hess used technology and specialized staff to craft a specific space within the hospital for this patient population. (10) Hess was well known for designing the "Hess incubator," which shared features with an oxygen chamber and was used to create an artificial environment and deliver oxygen therapy to premature infants. (11) He was also renowned for his book, *The Premature Infant: Its Medical and Nursing Care*, first published in 1941. Hess prioritized the role of the nursing staff in the premature infant nursery; Evelyn Lundeen, his nursing director, was the coauthor of the book. (10)(11) In the preface, Hess and Lundeen wrote that "Since it is our conviction that untiring, unremitting care has no substitute in the care of the premature infant, we have deemed it essential to give equal prominence to the role of the nurse," highlighting the significant value they placed in local, skill-based clinical knowledge in the care of this patient population. (10)

By completing medical school and her pediatrics residency at Johns Hopkins before heading to Harvard Medical School for a fellowship in the late 1950s, Avery would become both a product and perpetuator of the interdisciplinary transfer of knowledge between basic sciences in the laboratory and clinical practice in the hospital. She commented that, during her medical school years, the encouraging environment and value placed on research at Johns Hopkins helped her realize the potential to conduct clinical and "bench to bedside" research throughout her career. (12) Compounded with the need for more specialized, interdisciplinary care for newborns, this interface between the laboratory and clinic would lay the grounds for the fruitful collaboration that would emerge in the mid-20th century.

HMD AND THE COLLABORATION BETWEEN PEDIATRICS AND PHYSIOLOGY

Avery's curiosity about infant respiration and research on HMD was made possible by a wide-ranging network, encompassing pediatricians, obstetricians, physiologists, and other medical professionals, which focused on respiratory mechanics in the mid-20th century. Her interest in the lung arose from her personal experience with illness; in the early 1950s, after graduating from Johns Hopkins Medical School, Avery contracted tuberculosis. During her 2-year bout of illness, she grew intensely curious about the physiology of the lung, and HMD caught her attention. (2) She was inspired by the book *Physiology of the Newborn Infant* by the Harvard pediatrician Clement A. Smith, which covered newborn development and adaptations at birth as well as their effects on the establishment of regular respiratory processes. (9)(13) Avery would later train under Smith during her fellowship at Harvard Medical School, adapting his approach of combining pediatrics, physiology, and basic science endeavors to investigate breathing in newborns.

In 1957, Avery moved to Boston to undertake a fellowship at Harvard Medical School that was funded by the National Institutes of Health (NIH) and joined the research laboratory of Jeremiah Mead, Professor of Environmental Physiology at the Harvard School of Public Health. (1)(4)(14)(15) His laboratory had recently discovered that the surface forces of the lung were responsible for its elastic recoil, which led them to calculate a new value for the lung's surface area. (4)(16) In 1959, Avery and Mead published an article entitled "Surface properties in relation to atelectasis and hyaline membrane disease," which demonstrated surfactant deficiency to be the cause of HMD. (17) The article was published in the *American Journal of Diseases of Children* because Richard Day—then chairman of pediatrics at the University of Pittsburgh and Avery's friend of many years—was the editor of the journal and was excited about the connection between surface tension and lung function. He personally asked Avery to publish the article in his journal even though it had a significant physical-chemical focus and clinical research methodology was lacking. (12)

Avery's collaboration with Mead built on the work of pioneer physiologists such as the Swiss physician Fritz Rohrer, who, beginning in 1915, developed quantitative measurements for use in various areas of respiratory mechanics. (18) In the 1940s, Sir Joseph Barcroft, a British physiologist, advanced the understanding of the fetus' transition from "placental to pulmonary respiration."(6) In addition, Avery was inspired by the body of work conducted by Wallace Fenn, Hermann Rahn, and Arthur Otis at the University of Rochester between 1941 and 1956. (18)(19)(20) Although it was not their initial area of interest, these 3 Rochester physiologists were motivated to study respiratory issues because of the use of chemical gases during wartime. They undertook studies that elucidated the mechanisms behind pulmonary gas exchange; the effects of altitude, hyperventilation, and pressure breathing; and identified the relationship between pressure and volume as they related to the lung and chest wall. (21) In a lecture entitled "First Breath," which she delivered in 1959, Avery commented on the work of these physiologists and others, noting that their efforts "had an impact on pediatrics in recent years as those concerned with resuscitation of newborn infants have become aware of the concepts and tools recently applied." She explained that "Paralleling the intellectual revolution in respiratory physiology and the technological advances, pediatricians interested in newborn infants and pathologists have become aware of the frequency of respiratory failure as a cause of neonatal death." (19) This respiratory failure became a research interest for medical practitioners with a range of backgrounds.

The concept of research collaborations across the demarcations of medical specialties was becoming commonplace during the time of Avery's work, with neonatal centers being generously funded by sources including the NIH, the March of Dimes, and the Robert Wood Johnson Foundation. (22) This shift in investigational approaches to neonatal diseases was made possible by what Avery described as "the changing status of medical investigation in this country" in the preface to her 1964 monograph on the newborn lung, *The Lung and its Disorders in the Newborn Infant*. (15) Avery implied that the research of her predecessors was stringently regulated by the objectives of their preexisting research programs or clinical practices. In contrast, Avery felt that she was not bound to any such research agenda: "I have been relatively free to pursue investigations as they seemed appropriate, and to read at length, with only as many clinical and teaching responsibilities as were important to stimulate the investigative ones."(15)

Avery's inclination to follow diverse research leads during her time at Harvard was exemplified by her visit in 1957 to John Clements' laboratory at the Edgewood Arsenal in Maryland—an army research facility focused on basic sciences. The immediate impetus for Clements' research was the Soviet threat of using chemical weapons, which led to the military's studies on how nerve gases affect the human lung. Before Avery joined the Mead laboratory, Clements had heard of the group's findings on calculated lung surface area and was inspired to investigate surface tension in the lungs as well as the material that he believed maintained low surface tension in the alveoli. (4)(23) In addition to Clements, Avery carefully followed the work of Richard Pattle, a researcher at the Chemical Defense Establishment in England who, like Clements, based his investigations on gases used in war and their impact on the human lung. (4) While studying pulmonary edema, Pattle found that the healthy lung contained particularly stable "bubbles," leading him to the conclusion that the lung's internal surface was covered with a substance that had low surface tension. (4)(24) Clements used Pattle's findings in the mid-1950s and integrated them with the Mead group's calculation of lung surface area to determine the surface tension of the substance, which he ultimately termed *surfactant*. (4)(25) This back and forth among Clements, Pattle, and Avery and Mead crossed the borders between science aimed at biomedical cures and military research. Furthermore, it shaped the language used by the medical community when discussing surfactant and its vital role in HMD.

TRANSLATING THE PHYSICAL-CHEMICAL METHOD FOR PEDIATRICIANS

As Avery continued to adopt methodology and scientific insight from respiratory physiologists in the late 1950s, she also embraced their language and style of explaining experimental results. The physical-chemical method strongly influenced the ways in which she would present her work and the body of literature on lung surface tension, surfactant, and HMD to medical audiences. Delivering a talk in New Haven in April 1959, only 1 month ahead of her publication with Mead on the relation of surface properties of the lung to HMD, Avery concentrated on the subject of surface forces and included figures, such as pressure-volume curves, as well as multiple references to the Laplace equation to illustrate the relationship between surface tension and inflation of the alveoli. Although her notes were heavily grounded in basic science, Avery was careful to make periodic allusions to the subject matter's relevance to pediatrics and to remind herself to "translate" the topic for her audience of pediatricians. (26) While Avery's multiple connections between the physical-chemical presentation of her topic and the field of pediatrics might have served to bolster the audience's interest in her talk, it also demonstrated how pediatric medicine had gained a foothold in the 1950s as the medical specialty that held the most authority over the respiratory physiology of the neonate.

To isolate the factors that led to Avery's success in her research and the ultimate discovery of surfactant deficiency as the cause of HMD, one can look to Ian Donald, the Scottish obstetrician who initiated the use of diagnostic ultrasonography in the mid-1950s. (6) Although Donald's use of ultrasound technology was an important contribution to newborn medicine, his earlier work on tackling the breathing difficulties of neonates was less successful. During his time at the Department of Obstetrics at St Thomas' Hospital in London, Donald worked with Maureen Young, a protégé of the physiologist Sir Joseph Barcroft. Eventually, they developed an "automatic respiratory amplifier," which was designed to inflate the lungs by following the natural rhythm of the infant's breathing. The amplifier served as Donald's first major contribution to the field of respiratory physiology as a clinician-scientist, priming his subsequent ventures into neonatal respiratory distress and HMD. (6)

Donald's focus on HMD began in the early 1950s, after he joined the staff of the Royal Postgraduate Medical School at Hammersmith Hospital. Donald collaborated with Albert Claireaux, a pathologist at Hammersmith whose histologic observations of HMD helped elucidate its cellular pathology. (6) At the time, it was only possible to diagnose HMD on postmortem examination because the symptom of respiratory distress could also be related to primary atelectasis, among other causes. Ahead of his ultrasound investigations, Donald used his curiosity with medical imaging, specifically radiography, to test whether there were anatomic changes in the lungs of neonates that corresponded to the development of HMD. It was ultimately the lack of collaborations with those trained in biochemistry and physiology that caused Donald's research on HMD to be futile. Nonetheless, he and Claireaux concluded that a certain "mottling" of the lungs, distinguishable on radiographic imaging, correlated with the initial phases of HMD. (6)

The network of neonatal clinicians and researchers that emerged during the 1950s, which has been charted by Rachel McAdams, illustrates a web of collaborators that all shared a basic interest or formal training in pediatric medicine. (27) As Nicolson and Fleming assert in their textbook on ultrasonography, "The time when an obstetrician, working in the clinic, could provide leadership in the treatment of sick babies was rapidly passing."(6) In the context of research on neonatal respiratory distress in the 1950s, flexibility in methodology and collaboration across disciplines, which pediatricians were practicing, was as important as the research question being posed. While Donald took a clinico-anatomic approach to his studies, Avery's physical-chemical method, which was inspired by military scientists as well as classically trained physiologists, focused her interests on the inner workings of the lung. She transformed the clinician's understanding of this organ into an amalgamation of physical properties, allowing "surface tension," "surface area," and "elastic recoil" to become common terms shared with the audiences of her lectures and readers of her articles.

Just as the 1950s witnessed the development of a tightly knit neonatal network, the type of language used by this network changed in parallel. Avery recognized the need for a common language and clear communication between the different medical practitioners involved in this network, and appeared willing to fill the role of translator among the various groups. In the 1960 Ross Conference on Pediatric Research, she delivered a talk on the relationship between pulmonary mechanics and infant age and size. Commenting on the frequent partnership between pediatricians and physiologists that characterized research on neonatal respiration at the time, she asserted that:

> "When physiologists and pediatricians meet it is important that they communicate first of all some facts. On the strength of these, the theories must stand, or fall, or perhaps today be formulated de novo. My role as an 'introducer' this morning is to present some of the facts which must intrigue physiologists and indeed are the reason-to-be of pediatrics, namely the special adaptations of the small, growing organism."(28)

Avery positioned physiologists as having much to learn from pediatrics as far as their interest in neonatal respiration was concerned. Her explicit reference to pulmonary mechanics and their relation to the growing newborn as being the "reason-to-be" of pediatric medicine placed the research topic squarely within the jurisdiction of pediatrics, with physiology providing the necessary methodologic assistance for investigations. As a female physician and researcher in the 1950s and 1960s, Avery had to navigate a male-dominated field in a tactful way for her voice and work to be granted attention. As she explained, "It's been the pattern of my life to go ferret out people who are smarter than I am, and then sit around and learn what they have to say, and put it together." In the case of her work on surfactant deficiency, Avery prided herself on being "the glue for all of this," asserting that "the ideas were all there waiting to be glued together. I think of it as analogous to a jigsaw puzzle [...]." (12) Although serving as the glue required a substantial amount of explanatory labor on Avery's part, taking on this role at medical conferences and through collaborations in her work allowed for networking and professional growth as a young female physician at this time.

RECONSTRUCTING THE NEONATAL PATIENT

Apart from shaping the direction and output of Avery's research, the neonatal research network also enabled the refinement of the clinical subject of its research projects: the neonatal patient. Despite its later prominence, it was initially difficult to convince the medical community of the findings in Avery and Mead's 1959 article that declared the association between surfactant deficiency and HMD. Their results represented a marked departure from the view at the time of HMD as an obstructive disease caused by the presence of membranes in the airways. Thus, there was a hesitation to affirm that the article demonstrated a cause-and-effect relationship between surfactant deficiency and HMD. (4)(12)(17) As word of Avery's findings spread during the 1960s, she was proactive in conducting follow-up studies to definitively draw the line between the surfactant system and its necessity in maintaining homeostasis in the lung. At the same time, she traveled across the world delivering lectures to convince the scientific community of the validity of her research. (4) These roles catapulted her to the forefront of the emerging field of newborn medicine, consisting of "clinicians, clinician-scientists, and basic scientists."(4) Moreover, her ability to serve as an introducer and translate specialized knowledge between these different groups added value to her professional reputation. With increasing recognition of Avery as a leading expert in HMD, or as it was increasingly beginning to be known, "respiratory distress syndrome," she played a role in shaping new understandings of the neonatal patient. As this modification of the neonate took place during the 1960s and 1970s, the field of neonatology and its practitioner, the neonatologist, was born. (27)

Between 1960 and 1966, Avery participated in a number of conferences and informal colloquia organized around pediatric research topics as well as those in adult medicine and professional development. Avery was asked to introduce the topic of "Mechanics of Respiration" at the 37th Ross Conference on Pediatric Research in 1960, only 1 year after publication of her widely cited article with Mead. During these conferences, the Ross Laboratories of Columbus, OH, sought to shift the relationship between the pharmaceutical industry and the medical community by "assist[ing] in the correlation of the latest information from research on subjects of general interest in the practice of pediatrics, and to stimulate further research by the exchange of information."(29) The Ross Laboratories' lack of a personal stake in the conference topics allowed the academic medical centers to mold the direction of the talks, and, in turn, the larger trends in pediatric medicine at the time.

In 1959, 2 months after Avery's publication, an "informal discussion" on the proper name for HMD took place among participants at the IX International Congress of Pediatrics in Montreal, Canada. Clement A. Smith, the physician with whom Avery had worked during her NIH fellowship in Boston, was one of the chairs of the discussion. Despite being in attendance, as well as having her name and work on surfactant referenced several times, Avery did not voice her opinions during the discussion. This was likely because she was 1 of only 7 women in a room of 35 physicians and did not want to speak out of turn as a junior physician, despite her expertise. (30) Ultimately, "idiopathic respiratory distress of the newborn" was the frontrunner classification after the physicians voted.

In 1963, Avery used the term *pulmonary distress syndrome* at the "Advanced Seminar in Pediatrics: Fetus, Premature, and Newborn Infant" conference that was hosted by the University of California, Los Angeles (UCLA) School of Medicine. (31) Her terminology removed the "newborn" designation while retaining the term "distress"—2 decisions that subtly shifted the disease away from being understood as applicable to all newborns, as well as assigning "distress" to the patient it affected. The UCLA conference was also significant for its explicit reference to the distinction between fetuses, premature newborns, and term newborns, placing these patients on a differentiated, chronologic timeline of development. Although the conference predated the politics behind defining fetal personhood, it presented the fetus as a discrete phase of development and separated the schedule of talks into the following categories: "Maternal-Fetal Relationships," "Normal Newborn Physiology," "Diseases of the Newborn Prematurity," and "Diseases of the Newborn." (31)(32)

Avery also participated in the National Institute of Child Health and Human Development's "Interdisciplinary Conference on Neonatal Respiratory Adaptation" in 1963. This conference brought together pediatricians, obstetricians, physiologists, and other researchers to discuss intrauterine events, the transition from intrauterine to extrauterine life, and postnatal adaptations. (33) Avery's mentor during her Boston fellowship, Clement A. Smith, was the discussion leader for the "Postdelivery Adaptation and Maladaptation" session, and asked her to contribute to the session by "starting off from [her] analogies with space medicine as gravitational changes affect the movement of water in the body." (34) The space medicine analogies that Smith referred to were part of a prior talk in which Avery had declared that "we who are concerned with newborn infants have much to learn from space research" due to the need to "ponder hydrostatic mechanisms in the lung and their role in the formation of atelectasis and edema, to relate oxygen toxicity to the duration of exposure and to the Po_2 in the blood, [and] to worry about perceptual deprivation" that existed in both lines of work. (35)(36) In asking Avery to use this analogy again, Smith spoke to the success of the analogy in inciting audience interest.

Avery's reputation extended beyond the medical community; in 1963, Patrick Bouvier Kennedy was born 5½ weeks premature to President John F. Kennedy and Jacqueline Kennedy Onassis. Kennedy lived for only 39 hours after delivery and, for the majority of lay people, he was their first encounter with HMD. Following the news of Kennedy's premature birth, Avery was consulted by journalists across the country. (37)(38) She explained that "the respiratory disease hyaline membrane usually increases in severity over the first 24 to 48 hours, then either leads to death or gradual recovery," thereby providing an expert opinion on the Kennedy infant's prognosis. (38) Although Avery took the opportunity to assert the severity and significance of HMD, she was surprisingly wary of citing findings from her own research that linked the cause of HMD to surfactant deficiency.

One space in which Avery had complete control over the presentation of the neonate was in her monograph, *The Lung and its Disorders in the Newborn Infant*. The first edition of the book was published in 1964 while Avery was an assistant professor at Johns Hopkins. By this point, the pediatrician Alexander Schaffer—who wrote the foreword for Avery's book and was also the consulting editor—had already coined the terms "neonatology" and "neonatologist." (15)(27) His definition deemed neonatology to be the specialty that "designates the art and science of diagnosis and treatment of disorders of the newborn infant," a description that Avery's book clearly matched, specifically through its investigation of matters related to the lung. (39)

The late 1960s to mid-1970s also led to the creation of physical spaces in hospitals that further demarcated the neonatal patient population. The concept of a space dedicated to the interprofessional care of newborns was not necessarily new; Julian Hess had previously constructed a premature infant nursery in 1922 at Sarah Morris Children's Hospital in Chicago. The nursery was renowned for its 28 incubators, which were considered to be the most sophisticated of their kind, as well as its integration of nurses in the care of the premature infants. (11) By relabeling the premature infant nurseries as "intensive care" units, hospitals conveyed the idea that they placed a significant value on the neonatal patient and the type of clinical work that was being done in these units. As the neonatal patient population became more clearly defined, the neonates received care "based on age and unique medical needs rather than diagnosis." (40) The expansion of NICUs in the United States aligns with the increased research interest and efforts directed at HMD. With their abundance of ventilators to provide oxygen support as well as other highly technical medical equipment, these NICUs became areas for the treatment of neonates whose specialized needs were being defined in tandem with the development of new research and medical therapies. (40)

CONCLUSION

Between 1974 and 1985, Avery served as the first female physician-in-chief of Boston Children's Hospital. (14) As a pediatrician and researcher, Avery focused on the neonatal patient population in her work, and as she rose to prominence for her findings, she reinforced the placement of the care of this patient within the realm of pediatrics. Avery was never deemed a neonatologist, because the specialty did not officially exist until 1975, when the American Board of Pediatrics created the Subspecialty Board of Neonatology. Her work on HMD, coupled with the new technological advances in hospital-based medicine in the late 20th century including prenatal diagnostic techniques such as amniocentesis and fetal ultrasonography, framed newborns as distinct, vulnerable patients in need of hospital-based care, and whose diseases ought to be subject to biomedical investigations. The refinement of this patient population in the United States during the early 1960s gave way to the creation of a new space for premature and ill full-term newborns: the NICU. (41)

Avery's frequent collaborations with physiologists and basic science researchers perpetuated a culture of interdisciplinary collaboration within newborn medicine, a culture that was instrumental in "biomedicalizing" the care of neonates. As a young female physician, Avery operated within her professional settings in a unique way that allowed her to make an impact without challenging senior physicians, which facilitated her contributions to neonatology and respiratory physiology. By being involved in a number of steps in the research process—from studying minced lungs to being present for a newborn's first breath in the delivery room—Avery integrated the work being done in the laboratory with that being done in the clinic. (12) She shared her insights with medical audiences at conferences, framing her role as that of a translator between both pediatricians and physiologists, as well as between those who practiced the physical-chemical methods of investigation and others who preferred the more traditional, clinicoanatomic ones. Mary Ellen Avery's research in HMD made her a well-known figure in medicine, facilitating her contributions to the development of the clinical field of neonatology and the critical practice of applying basic science research to the patient.

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Historical Perspectives: Beyond the First Breath: Hyaline Membrane Disease and Constructing the Neonatal Patient, 1959–1975

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Enteral Feeding of the Preterm Infant

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Education Gaps

1. Clinicians should be able to initiate and advance enteral feedings for the preterm infant safely and effectively.
2. Clinicians should recognize the importance of appropriate enteral feeding and early nutrition for the long-term growth and neurodevelopment of preterm infants.

Abstract

Premature infants commonly suffer from extrauterine growth restriction from inadequate nutrition and the loss of the last months of gestation, a critical period for brain and body growth. Providing optimized nutrition for the premature infant is a crucial task of the neonatologist and has a significant impact on the future growth and neurodevelopment of these infants. Enteral feeding is nuanced in the preterm population and requires specific knowledge of the nutritional requirements of the preterm infant and the various substrates and methods available to achieve proper nutrition.

Objectives After completing this article, readers should be able to:

1. List the macronutrient requirements of the preterm infant.
2. Describe the nutritional composition of human milk, donor breast milk, and preterm infant formula.
3. Recognize the benefits of human milk for the preterm infant and that preterm and term human milk have different compositions.
4. Recognize that human milk needs to be fortified to meet the nutritional needs of preterm infants and describe how standard infant formulas are altered to meet the needs of preterm infants.
5. Explain advantages and disadvantages of the use of donor human milk.

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ABBREVIATIONS

BUN	blood urea nitrogen
CA	corrected age
EUGR	extrauterine growth restriction
GA	gestational age
HM	human milk
HMF	human milk fortifier
NEC	necrotizing enterocolitis
PMA	postmenstrual age
VLBW	very low birthweight

INTRODUCTION

The last months of gestation are characterized by rapid growth and brain development. Infants born prematurely are deprived of this experience. It is not surprising that most preterm infants experience extrauterine growth restriction (EUGR) and are at risk for developmental delays. Appropriately feeding the preterm infant is one of the most crucial tasks of the neonatologist.

Most infants born at 24 to 29 weeks' gestation experience EUGR and their weights are at less than the 10th percentile at discharge or 36 weeks' postmenstrual age (PMA). There are many reasons for this inadequate growth. The nutritional needs of the preterm infant are not fully understood, so it is difficult to know what to provide and how to do so. Even when good nutrition is prescribed, the infant may not actually receive the full benefit because feedings may be suspended or other complications may ensue. Preterm infants have increased metabolic demands from illness severity and respiratory distress, which affect their ability to absorb and use nutrients. They often have decreased gut motility and poor tolerance of enteral feeding from medication exposure and underdeveloped gut mucosa. An association between severity of illness, poor linear growth, and decreased fat-free mass has been documented. Poor early growth is associated with decreased neurodevelopmental and growth outcomes at 18 to 24 months' corrected age (CA), with early nutrition having an impact of 6 to 15 IQ points in various studies. Children are less likely to have growth parameters lower than the 10th percentile at 18 months' CA if higher in-hospital growth rates are achieved, as well as lower incidences of cerebral palsy, neurodevelopmental impairment (including blindness and deafness), Bayley and Psychomotor Development Index scores less than 70, and rehospitalizations. Faster weight gain has been reported in infants who receive fewer days of parenteral nutrition, initiate enteral feedings sooner, and attain full enteral feedings earlier. Increased severity of illness, particularly the need for mechanical ventilation during the first week of life, greatly influences decisions about early feeding. Less critically ill infants are given significantly more enteral and parenteral nutrition during the first 3 weeks after birth. There is no evidence to support limiting any form of nutrition in infants receiving mechanical ventilation.

Poor nutrition may reduce immune competence and decrease energy stores, rendering preterm infants more susceptible to infection and less able to recover from acute and chronic disease. Lack of enteral nutrition causes gastrointestinal mucosal atrophy and leads to decreases in protective mucus, decreased enzyme activity, and increased gut permeability. These findings may cause dysfunction and feeding intolerance, and are associated with a greater risk for necrotizing enterocolitis (NEC). Enteral nutrition is paramount for gastrointestinal growth and development. Early enteral feeding decreases the time to reach full feeding volume, as well as length of stay without increasing NEC or serious infections. Enteral feeding should not be initiated in infants who are hemodynamically unstable or have severe left-to-right ductal shunting, abnormal gastrointestinal examination, bilious gastric fluid, severe metabolic acidosis, sepsis, or hypoxemia.

GOALS OF ENTERAL NUTRITION

Extreme prematurity is a nutritional emergency. Fetal body composition and size at various stages of gestation are used as a reference standard for extrauterine growth and accretion rates of protein, fat, and minerals for preterm infants. Optimal nutrition should maintain lean body mass and bone density, maximize neurodevelopment, minimize complications (NEC, chronic lung disease, and infection), reduce postnatal weight loss with earlier return to birthweight, and improve catch-up growth. The targeted weight gain is 18 g/kg per day, head circumference growth of more than 0.9 cm/week, and length gain of 1 cm/week. The smallest and least mature infants need the most protein, but energy needs escalate with increasing body weight. Early protein intake is a major contributor to improved weight gain velocity and a decreased risk of neurocognitive impairment. For appropriate growth, a caloric goal of 120 kcal/kg per day and protein goal of 3.8 g/kg per day are recommended in very low birthweight (VLBW) infants within the first 7 days after birth (Table 1). This amount of protein can only be provided through enteral fluid of more than 150 mL/kg per day of fortified human milk or "high protein" preterm formula. Infants born at less than 31 weeks' gestational age (GA) typically have an 18 g/kg protein deficit and 600 kcal/kg deficit by 14 days of age. Proportional growth, rather than absolute weight gain, should be monitored to evaluate growth. Many studies suggest that reduction in practice variation improves patient outcomes. The establishment of feeding guidelines reduces EUGR and achieves full feedings sooner. Consulting a neonatal specialist (registered dietitian or nutritionist) to make recommendations and monitor guideline compliance may facilitate nutritional success.

SUBSTRATES FOR ENTERAL FEEDING

Human Milk

The American Academy of Pediatrics recommends that preterm infants should exclusively receive human milk (HM), preferably from their own mothers if available, or if not available, pasteurized donor HM. Breastfeeding

TABLE 1. Nutritional Needs of the Preterm Infant

NUTRIENT	RECOMMENDATION (PER KG/DAY)
Energy	110–130 kcal
Protein	3.5–4.5 g
Fat	4.8–6.6 g
Carbohydrate	11.6–13.2 g
Calcium	120–200 mg
Phosphorus	60–140 mg

Adapted from Koletzko B, Poindexter B, Uauy R. Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. *Basel, Switzerland: Karger; 2014.*

provides developmental benefits that extend into adolescence. The use of exclusive HM when paired with standardized feeding guidelines can improve tolerance of feedings and decrease the incidence of NEC. Decreased rates of NEC have been seen with an exclusive HM-based diet compared with an HM-based diet supplemented with bovine milk–based products. The number needed to treat with exclusively fed HM is 10 to prevent 1 case of NEC, and 8 to prevent 1 case of "surgical NEC" or death. HM-fed infants have decreased rates of late-onset sepsis, urinary tract infection, diarrhea, and upper respiratory infection. The protection against NEC and sepsis appears to be dose-dependent. HM is also associated with decreases in the incidence and severity of retinopathy of prematurity, improved neurodevelopmental and visual outcomes, and improved feeding tolerance compared with formula. Improved tolerance allows infants to receive fewer days of parenteral nutrition, significantly decreases morbidity, and decreases length of stay.

HM contains bioactive factors that benefit growth and development. This includes improved immunity with antibacterial, antiviral, and anti-inflammatory effects. A healthy microbiome is promoted by the high oligosaccharide content of HM. The oligosaccharides have a prebiotic and antiadhesive effect. This blunts the intestinal inflammatory response to pathogenic bacteria. The gut of the HM-fed infant is colonized mostly by *Bifidobacteria* and *Lactobacilli* as opposed to the coliforms, enterococci, and *Bacteroides* species that colonize formula-fed infants. Abnormal colonization is also promoted by delayed enteral feeding, the use of broad-spectrum antibiotics, and exposure to the pervasive organisms in the NICU milieu. Maturation of the gastrointestinal tract is supported by components in HM resulting in improved motility, smaller gastric residuals, and decreased intestinal permeability. Preterm infants have decreased ability to absorb fats. Enzymes in HM allow for improved fat absorption and intestinal lipolysis.

Milk from mothers of preterm infants initially has higher protein and mineral content than term HM. Unfortunately, HM is slightly low in chloride and is deficient in protein, calcium, and phosphorus to meet the needs of the preterm infant. The content of preterm HM varies widely in protein and fat content depending on time of day, the individual mother, stage of lactation, time within a single expression of HM, method of collection, storage, and mode of enteral feeding. By 42 days of lactation, preterm milk protein content stabilizes at approximately 0.8 to 1 g/dL, which is similar to term milk.

Maternal HM

Pumping should be started as soon as possible after delivery. Initiation of lactation can be difficult so the advantages of breastfeeding should be emphasized, along with continued encouragement. Most hospitals in developed countries have lactation consultants to facilitate this. Skin-to-skin contact can increase the success of lactation. Breastfeeding mothers report feeling empowered, self-confident, and more bonded to their infants. Frequent milk expression throughout the day should be implemented; more than 100 minutes of expression per day is optimal. Electric breast pumps are more efficient than hand expression and should be made available to mothers. Mothers must be advised of the importance of colostrum.

Donor HM

For VLBW infants, if maternal HM is not available, pasteurized donor HM is preferred over formula. Many feeding guidelines recommend donor HM through 33 weeks' PMA to reduce the rate of NEC, which normally declines after 32 weeks. Pasteurization removes potentially harmful bacteria, but unfortunately also removes lipases, lymphocytes, and other beneficial components of HM. Analysis of pooled donor HM reveals a consistent content of approximately 0.9 g/dL protein and 4 g/dL fat, with an energy content of 48.3 kcal/100 mL.

Preterm infants fed donor HM demonstrate slower growth rates and biochemical abnormalities that suggest insufficient protein and mineral intake. Decreased weight gain is observed when infants receive larger amounts of milk and more nutritional supplements. Despite these shortcomings, donor HM is a valuable resource. Seventy-two percent of mothers of preterm infants are unable to provide all the milk needed for an exclusive HM diet. Donor

HM costs $27 to $590 per NICU infant during hospitalization (based on an average price of $4/oz).

Premature Formula

Formula specifically designed for preterm infants is appropriate to use if maternal or donor HM is not available. The specific formulations are based on fetal accretion rates and studies of metabolism and gastrointestinal tract development. Premature formula provides greater amounts of protein, calcium, zinc, iron, phosphorus, and copper than term formula without exceeding the overall energy intake goal (Table 2). Despite sodium content being higher than HM or standard infant formula, some infants may still require supplementation. Premature formula is composed mainly of whey, rather than casein, reducing the frequency of metabolic acidosis. Compared with standard formula, the protein content is 50% greater and provides 3 to 4 g/kg per day. This improves weight gain and protein accretion. Vitamin concentration is also higher. Fat content is provided by nearly equal quantities of long-chain and medium-chain triglycerides. Preterm infants have a relative lactase deficiency, and premature formula has a lower lactose concentration. Standard premature formula has low iron concentration (3 mg/L), but higher iron versions are available that provide 15 mg/L, which is optimal for a discharge formula. Use of premature formula results in higher verbal IQ scores (even into adolescence) than when term formula is used for preterm infants.

Infants with a birthweight of less than or equal to 1,800 g and GA of less than or equal to 34 weeks at birth with no available HM or needing HM supplementation should be provided 24 kcal/oz premature infant formula. This formulation is iso-osmolar. Infants who are volume restricted or have inadequate growth may benefit from hypercaloric formula. Ready-to-feed 30-calorie preterm formula is available. It reduces mixing errors and eliminates powdered formula use in this immunocompromised population. It provides the same amount of protein as standard preterm formula but in less volume and has more calories from fat and less calories from carbohydrates. The osmolality of 30 kcal/oz ready-to-feed formula is 325 mOsm/kg of H_2O.

FORTIFICATION

Human Milk Fortifiers

HM does not provide adequate nutrients for optimal growth. Fortification is needed, especially to meet protein needs. Fortification provides additional protein, calcium, phosphorus, vitamin D, and sodium. Human milk fortifiers (HMFs) vary in micronutrients because the requirements of premature infants for most micronutrients are only approximated. Multicomponent HMFs improve postnatal weight gain, linear growth, and brain growth.

Because of the variable composition of HM, appropriate fortification, especially of protein, is challenging and often inadequate, resulting in EUGR. Fat content can also be decreased by the collection, storage, and administration of HM, resulting in lower energy content. HM analyzers can help optimize fortification. Only 76% of the total nitrogen in HM is true protein, so most analyzers overestimate protein content by about 24%. If a milk analyzer is not available, fortification can be adjusted based on blood urea nitrogen (BUN) concentration (goal: 3.2–5 mmol/L) as a surrogate for adequate protein supply. While custom fortification may provide more appropriate amounts of nutrition to an individual infant, generalized fortification strategies are simpler and less prone to error. HMFs provide additional protein from either cow milk fractions or donor HM. Fortification increases the osmolality by 35 to 95 mOsm/kg H_2O, which can be further increased if the fortified milk is left standing.

Fortifiers are available as powders or liquids in premeasured quantities, which are added to specific volumes of HM. No significant long-term adverse effects due to HMFs have been reported. The higher osmolality resulting from the addition of HMF has not been associated with NEC or intestinal injury. Introduction of fortification can slow

TABLE 2. **Nutrition Provided by Unfortified Substrates**

Per 100 mL	kCal	PROTEIN (g)	FAT (g)	CHO (g)	Ca (mg)	P (mg)
Preterm human milk	67	1.4	3.8	6.5	24.4	12.5
Donor milk	65–67	0.9–1.2	3.2–3.6	7.2–7.8	24.4	12.5
Preterm formulas (24 kcal/oz)	80	2.4	4–4.3	8.1–8.7	130–143	66–79

CA=calcium; CHO=carbohydrate; P=phosphorus. From Adamkin DH. Nutritional Strategies for the Very Low Birthweight Infant. *New York, NY: Cambridge University Press; 2009.*

gastric emptying and cause increased residuals. The antibacterial activity of HM can be diminished by added iron in fortifiers.

Fortification to prevent poor growth and osteopenia should be started in infants of less than 32 weeks' GA or less than 1,500 g birthweight. Appropriate fortification must be initiated no later than when HM enteral feedings reach 100 mL/kg per day but may be started as early as 50 mL/kg per day. Fortification of even the first feed has been well-tolerated. When using donor HMF, fortification can be started at low volumes, such as at 40 mL/kg per day. Some NICU feeding guidelines initiate fortification at half strength and advance to full strength; however, it is more commonly started at full strength.

HM can be mixed with 24 kcal/oz preterm formula to make 22 kcal/oz formula with enhanced nutrients. Portions of a 30 kcal/oz ready-to-feed liquid premature formula can be added to HM to make 24 or 25 kcal/oz feeds with the added benefit of avoiding nonsterile powders. As this practice dilutes the HM, the benefits of HM theoretically may decrease (Table 3).

Powder Fortification

Historically, there has been a fear of "high" protein content in premature formulas. These concerns arose after a study in the 1970s demonstrated that high quantities of poor-quality protein (6–7.2 g/kg per day) increased the risk of neurodevelopmental impairment. Powder fortifiers were developed during this era and provide 1 to 1.1 g/dL of protein, levels that do not meet the protein needs of preterm infants. The Academy of Nutrition and Dietetics and the Centers for Disease Control and Prevention do *not* recommend the use of powdered formula fortification in the NICU because of the potential for infectious complications.

Liquid Fortifiers

Bovine milk–based fortifiers add 1 to 1.8 g/dL of protein. HM-based liquid fortifier adds 0.6 g/dL of protein when mixed at 80 kcal/dL. However, the amount of protein added increases as the ratio of fortifier to milk increases and can be as high as 1.6 g/dL when it is mixed 1:1 with HM, resulting in a 100-kcal/dL formula. The dilution of HM increases as fortification increases. Commercially available HM donor milk has +4, +6, +8, and +10 formulations to provide 24 to 30 kcal/oz of protein. Liquid fortification results in better weight, head circumference, and linear growth without differences in tolerance or days to achieve full feedings. Liquid fortification is associated with increased prealbumin, albumin, and BUN but does not appear to increase the incidence of NEC or sepsis.

HOW TO GIVE ENTERAL FEEDINGS

Initiating and Advancing Feedings

There is no consensus on the best approach to provide enteral feedings to a preterm infant. However, there are basic principles. Minimal enteral nutrition/trophic feedings/gut priming are small feedings of less than or equal to 24 mL/kg per day and are thought to promote gastrointestinal maturation, reduce mucosal atrophy, and protect against NEC. Trophic feedings should be started as soon as possible. They are usually given for 1 to 3 days or more, depending on clinical status. Typically, only small amounts of colostrum are available for several days after birth. In such cases, clinicians should consider supplementing with donor breast milk or preterm formula. Ideally, enteral feedings should be started within 48 hours of birth, with delays up to 72 hours because of parental request to await the mother's own milk production. Delays in initiation of enteral feedings may occur because of clinical reasons,

TABLE 3. **Nutrition Provided with Different Commercial Human Milk Fortification Strategies**

Per 100 mL	kCal	PROTEIN (g)	FAT (g)	CHO (g)	Ca (mg)	P (mg)
PTHM + SSC30 (4:3 ratio, 24 kcal/oz)	80	1.7	4	5.6	72	40
PTHM + SHMF (1 pkt/25 mL, 24 kcal/oz)	80	1.9	3.3	6.7	112	63
PTHM + EHMF (1 pkt/25 mL, 24 kcal/oz)	80	1.8	3.8	5.6	77	42
PTHM + SSC30 (1:1 ratio, 24 kcal/oz)	83	1.9	4.2	6.2	84	47
Prolacta +4 (25 kcal/oz)	100	2.3	4.9	7.3	128	70

CA=calcium; CHO=carbohydrate; EHMF=Enfamil® Human Milk Fortifier; P=phosphorus; PTHM=preterm human milk; SHMF=Similac® Human Milk Fortifier; SSC30=Similac® Special Care®.

Adapted from Adamkin DH. 2009. Nutritional Strategies for the Very Low Birthweight Infant. *New York, NY: Cambridge University Press.*

such as treatment with vasopressor agents in a severely ill premature infant.

Advancement of feedings by increments of 20 to 30 mL/kg per day is reasonable for 1,000 to 1,499-g birthweight infants. However, for those weighing less than 1,000 g, lower volume advancement is generally used. Nevertheless, slower rates of advancement (<24 mL/kg per day) have not been shown to reduce the risk of NEC in VLBW infants. Faster advancement (up to 35 mL/kg per day) shortens the time to achieve full feedings and regain birthweight without increasing NEC. Feedings should be advanced with goals of achieving an enteral volume intake of 150 to 160 mL/kg per day, as well as 110 to 130 kcal/kg per day energy and 3.5 to 4.5 g/kg per day protein.

Bolus versus Continuous Feedings

Studies have failed to demonstrate differences between bolus and continuous feedings for VLBW infants. Systematic reviews comparing these methods have shown no differences in time to achieve full oral feedings, length of stay, NEC incidence, or postnatal growth rate. However, in infants weighing less than 1,250 g, continuous feedings may improve weight gain and lead to earlier discharge. Traditionally, gavage tube feedings were given as intermittent boluses using gravity for 10 to 30 minutes every 2 to 3 hours. Studies suggest that feedings every 2 hours improve feeding tolerance and reduce the time to achieve full volume. For some infants, especially those with feeding intolerance, slow bolus feedings for 30 to 120 minutes may be better. Continuous infusions can lead to fat loss, with up to 30% of the energy lost in the tubing. However, for VLBW infants, continuous feedings have been used to decrease energy expenditure, improve gastrointestinal maturation, reduce reflux, and improve feeding tolerance.

Route of Feeding

Prolonged gavage tube feeding is often necessary for preterm infants secondary to neurologic immaturity. Systematic reviews have not found benefits of nasal versus oral gavage tube placement. Transpyloric feeding should generally be avoided when possible, because it has been associated with increased mortality and gastrointestinal disturbances. This may be due to bypassing gastric acids (which destroy bacteria). Non-nutritive sucking starting around 32 weeks' PMA can facilitate the transition from tube feedings to nipple feedings. Once breastfeeding begins, higher caloric supplementation may be needed to provide adequate energy and protein.

Assessing Intolerance

Gastric residuals do not have predictive value for feeding tolerance. They occur frequently in the neonatal period from gestationally appropriate physiologic slow gastric motility and are virtually always benign and not indicative of NEC. Abdominal examination (assessing for distention), pattern and consistency of stools, and other clinical findings are much more informative than residuals. Volumes less than 4 mL/kg or less than 50% of a feeding given 3 hours earlier are not indications to withhold or reduce enteral feeding unless other significant clinical signs are present. Occult blood in the stool, increased abdominal girth, high urine specific gravity, and delayed passage of meconium or stool are all typically minimal obstacles in initiating and advancing feedings. If enteral feedings are held to evaluate for NEC or another disease, they should be restarted as soon as the clinical status of the infant allows, even if it is only within a few hours.

CONCLUSION

Premature infants commonly suffer from EUGR from inadequate nutrition and loss of the last months of gestation, a critical period for brain and body growth. Providing optimized nutrition for the premature infant is a crucial task of the neonatologist and has a significant impact on the future growth and neurodevelopment of these infants. Enteral feeding is nuanced in the preterm population and requires specific knowledge of the nutritional requirements of the preterm infant and the various substrates and methods available to achieve proper nutrition.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the differences in the nutritional composition of human milk and infant formula.
- Recognize the effects of different methods of processing of human milk, such as freezing, pasteurization, sterilization, and microwaving.
- Know that human milk needs to be fortified in order to meet the nutritional needs of preterm infants.

Suggested Reading

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NeoReviews Quiz

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1. Early enteral nutrition is important for gastrointestinal growth and development and has been shown to improve weight gain in preterm infants. Which of the following statements regarding early enteral nutrition is FALSE?
   - A. The lack of enteral nutrition causes mucosal atrophy.
   - B. Early enteral nutrition decreases the time to reach full feeding volumes.
   - C. Early enteral nutrition decreases length of stay.
   - D. Early enteral nutrition is associated with a greater risk of necrotizing enterocolitis.
   - E. The lack of enteral nutrition leads to increased gut permeability.
2. The goals of enteral nutrition are to maintain lean body mass and bone density, maximize neurodevelopment, minimize complications, and optimize weight gain. Which of the following recommended targets for appropriate growth is correct?
   - A. A weight gain of 18 g/kg per day.
   - B. A head circumference growth of 0.5 cm/week.
   - C. A length gain of 0.75 cm/week.
   - D. A caloric goal of 90 kcal/kg per day.
   - E. A protein goal of 3 g/kg per day.
3. Pasteurized donor human milk is recommended over formula for very low birthweight infants. Which of the following statements regarding pasteurized donor human milk is correct?
   - A. Approximately 50% of mothers of preterm infants are unable to provide all the milk needed for an exclusive human milk diet.
   - B. The pasteurization process removes lymphocytes but preserves lipase levels in donor human milk.
   - C. The protein content of pooled donor human milk is typically similar to that of term milk.
   - D. Infants fed donor human milk demonstrate similar growth rates as preterm infants fed their own mothers' milk.
   - E. The use of pasteurized donor human milk is recommended through 35 weeks' postmenstrual age to decrease the risk of necrotizing enterocolitis.
4. Human milk contains many bioactive factors shown to be beneficial for growth and development. However, human milk is low in protein, calcium, and phosphorus; therefore, fortification is required to meet the nutritional needs of the preterm infant. Which of the following statements regarding human milk fortifier (HMF) is correct?
   - A. The use of HMF increases the osmolality by 150 mOsm/kg H_2O.
   - B. The introduction of HMF leads to faster gastric emptying.
   - C. Fortification should be held until feeds have advanced to 120 mL/kg per day and are well tolerated.
   - D. The antibacterial activity of human milk is not affected by the addition of HMF.
   - E. Bovine milk–based fortifier adds 1 to 1.8 g/dL protein.

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5. Enteral nutrition is very important to optimize outcomes in preterm infants. Although there is no consensus on the best approach to feed a preterm infant, which of the following basic principles regarding enteral nutrition in the preterm infant is correct?

   A. The terms *minimal enteral nutrition*, *trophic feedings*, and *gut priming* describe small feedings of no more than 10 mL/kg per day.
   B. Daily enteral feeding advancement of 20 to 30 mL/kg per day is reasonable in preterm infants with birthweights more than 1,000 g.
   C. Rates of advancement of less than 24 mL/kg per day have been shown to decrease the risk of necrotizing enterocolitis.
   D. Trophic feeds for a minimum of 5 days are recommended to promote gastrointestinal maturation, reduce mucosal atrophy, and protect against necrotizing enterocolitis.
   E. Enteral feedings should be advanced to a maximum enteral volume intake of 130 to 140 mL/kg per day.

Enteral Feeding of the Preterm Infant

Kate D. Brune and Steven M. Donn

NeoReviews 2018;19;e645

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Probiotics, Prebiotics, and Synbiotics for Preterm Neonates

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Education Gaps

1. While the effectiveness of administering probiotics to prevent necrotizing enterocolitis in preterm neonates has largely been established, concerns regarding their safety and the delineation of the optimal formulation currently limit their widespread use.
2. Prebiotic substrates present in human breast milk promote colonization with commensal organisms conferring health benefits; whether these benefits can be achieved by adding these substrates to formula remains to be determined.

Abstract

Probiotics have been extensively studied in neonates over the past several decades. Multiple meta-analyses have found probiotics to be effective at decreasing the number of necrotizing enterocolitis incidents. While relatively few NICUs in the United States are routinely using probiotics, many NICUs around the world have been doing so for more than a decade. The barriers to the routine use of probiotics include safety concerns and the lack of a clear consensus on the preferred formulation, dosage, and duration. Further research must be done to determine the safest and most effective formulation. This article discusses the history of probiotics, mechanisms of protection, available clinical evidence, and barriers to the use of probiotics in neonates. This review also addresses the current state of evidence regarding the naturally occurring substances called *prebiotics*, which can be added to formulas in the form of a supplement to promote intestinal colonization with commensal organisms, and *synbiotics*, which are combination products containing both probiotic cultures and prebiotic substrates.

Objectives

After completing this article, readers should be able to:

1. Define probiotics, prebiotics, and synbiotics.
2. Describe the rationale for the use of probiotics, prebiotics, and synbiotics in neonates.

AUTHOR DISCLOSURE Dr Kona was the site principal investigator and received grant support for the research study: "A randomized, double blind, parallel-group, dose escalation placebo-controlled multicenter study to investigate the safety and tolerability of IBP-9414 administered in preterm infants." Dr Matlock has disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
CI	confidence interval
ELBW	extremely low birthweight
LBW	low birthweight
NEC	necrotizing enterocolitis
RCT	randomized controlled trial
RR	relative risk
VLBW	very low birthweight

3. Review recent findings from the published literature pertaining to probiotics, prebiotics, and synbiotics.
4. Describe barriers to the routine administration of probiotics to neonates.

INTRODUCTION

The term *probiotics* refers to live microorganism cultures taken or administered in an effort to confer health benefits. Formulations of these organisms have been investigated to determine their usefulness when given prophylactically to treat or prevent disease in neonates. Necrotizing enterocolitis (NEC) is a devastating disease, affecting about 7% of very-low-birthweight (VLBW) infants, and is one of the major causes of mortality and morbidity in preterm infants. Mortality from NEC ranges from 20% to 30% with the highest incidence among infants requiring surgical intervention. (1) The most feared complication of NEC is bowel resection, which ultimately leads to several complications, including but not limited to, short bowel syndrome, parenteral nutrition-associated liver disease, sepsis, and adverse neurodevelopmental outcomes. In addition, the financial burden of caring for infants with NEC is enormous and is estimated to cost between $500 million and $1 billion per year in the United States. (1)

NEC is the result of a multifactorial process of intestinal inflammation and damage involving abnormal intestinal colonization and bacterial overgrowth. (1) With abnormal intestinal colonization heavily implicated in the pathophysiology of NEC, it is unsurprising that probiotics have been investigated as a means to prevent this disease and with promising results. Currently in American NICUs, however, safety concerns and the availability of optimal proven formulations are limiting the widespread and routine administration of probiotics to preterm newborns. (2)

HISTORY

Elie Metchnikoff first described probiotics to be beneficial in 1908 when he wrote about a group of Bulgarians whom he felt owed their long, healthy lives to the bacteria they consumed in fermented dairy products. (3) *Lactobacillus* was administered to neonates as early as 1952 to examine its effect on weight gain. (4) In 1986, the first randomized controlled trial (RCT) of probiotics in neonates examined their effect on colonization rates with antibiotic-resistant bacteria. (5) The first large study of probiotics to prevent NEC was published in 1999 and showed a significant decrease in both NEC and NEC-related mortality compared with historical controls. (6) A flurry of trials followed these promising results, and the first meta-analysis of the use of probiotics to prevent NEC was published in 2007.

PROBIOTICS

Mechanisms of Protection

- Enhanced gut barrier function preventing pathogenic bacterial migration: Probiotics increase the production of mucus, secretory immunoglobulin A, and other bioactive factors, which decrease gut permeability to pathogenic organisms.
- Decreased colonization with pathogenic microorganisms and increased diversity: Probiotic organisms compete for the same space, binding sites, and nutrients as pathogenic microorganisms. Probiotics increase diversity and colonization with nonpathogenic microorganisms by secreting antimicrobial peptides and bacteriocins that inhibit the growth of other bacteria.
- Modified host immune response: In addition to augmenting the immunoglobulin A response, probiotics act via toll-like receptors to modulate the production of cytokines and inhibit apoptosis and stimulate cell regeneration.
- Increased enteric nervous system maturation: Probiotics promote improved gastrointestinal motility, which is a potential explanation for their beneficial effects in the prevention of NEC. (3)(7)

Probiotic Strains. In a 2015 phone survey of American NICUs, 16 commercial probiotic products were found to be used at the 70 centers administering them. Only 4 of the 16 products in use had undergone clinical trials specifically supporting their use in infants. Therefore, as of 2015, 90% of the probiotics currently in use in the United States have not been evaluated for safety or efficacy in preterm neonates. The most commonly used species are *Lactobacillus* and *Bifidobacterium*. *Bacillus* species have been used, but have also been the most often implicated in invasive infections. Brand names and species included for the most commonly used probiotic products in the United States are listed in the Table. (2)

Probiotics for Preventing NEC

By far, the most compelling indication for the use of probiotics in preterm infants is for the prevention of NEC. Numerous systematic reviews and meta-analyses of RCTs involving more

TABLE. **Probiotic Products Used in American NICUs**

PROBIOTIC BRAND NAME	SPECIES INCLUDED	AMERICAN NICUs USING PROBIOTICS
Culturelle	*Lactobacillus rhamnosus GG*	27%
Biogaia	*Lactobacillus reuteri*	14%
Gerber Soothe	*L reuteri*	14%
Florababy	*Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium bifidum, Bifidobacterium longum* *L rhamnosus*	9%
Align	*B infantis*	7%
Floro-Q2	*Lactobacillus acidophilus* *Lactobacillus paracasei* *Bifidobacterium* *Streptococcus thermophilus*	7%
Risaquad	*L acidophilus* *L paracasei* *Bifidobacterium* *S thermophilus*	6%
VSL#3	*B breve, B longum, B infantis* *L acidophilus, Lactobacillus plantarum, L paracasei, Lactobacillus bulgaricus* *S thermophilus*	6%
Lactinex	*L acidophilus* *L bulgaricus*	4%
ABC Dophilus	*B infantis* *S thermophilus* *B bifidum*	3%
Udo's Choice	*Lactobacillus casei, L rhamnosus, L acidophilus* *B infantis, B bifidum, B breve*	3%
Basid	*B bifidum* *L acidophilus* *L bulgaricus* *S thermophilus*	1%
Floratummys	*Bifidobacterium lactis* *L acidophilus*	1%
Life Start	*B infantis*	1%
Probiotic 123	*B bifidum* *B lactis* *L acidophilus*	1%
Tri-dophilus	*L acidophilus* *B bifidum* *B lactis*	1%

Adapted with permission from Viswanathan et al. (2)

than 10,000 neonates show that probiotics significantly reduce both risk of severe NEC (≥stage 2) and mortality. (8)

In a Cochrane review in 2014, AlFaleh and Anabrees showed a significant reduction in severe NEC among VLBW infants in the probiotics group when compared to controls (relative risk [RR] 0.41; 95% confidence interval [CI] 0.31-0.56) (17 RCTs, 4,914 participants). (9) A subgroup analysis of only high-quality studies (11 RCTs) demonstrated similar findings of significant reduction in severe NEC in the probiotics group (RR 0.43; 95% CI 0.31-0.59). In 2016, an updated systematic review and meta-analysis was published by Sawh et al, which demonstrated a significant reduction in severe NEC in premature infants receiving probiotics (38 trials, 10,520 patients), as well as the subgroup of VLBW infants (29 trials, 9,507 patients). (8) (Fig). Nevertheless, an important finding in the Sawh et al trial was that probiotics were *not* effective in reducing the risk of severe NEC in the extremely low-birthweight (ELBW; <1,000 g) population (6 trials, 1,618 participants). (8)

A meta-analysis of observational studies by Olsen et al, (10) consisting of 12 studies with 10,800 premature (<37 weeks) or low-birthweight (LBW; <2,500 g) neonates, revealed a significant reduction in the incidence of NEC in the probiotic group (RR 0.55; 95% CI 0.39-0.78). Although the strength of evidence from this study is weaker compared with meta-analyses of RCTs, the findings are similar and contribute to the growing body of evidence supporting the use of probiotics for the prevention of NEC.

Unfortunately, among the RCTs of probiotics, there is significant heterogeneity in the study criteria with regard to probiotic species, single versus multiple species, dosage, time of initiation, duration, and the type of feed—human milk versus formula versus combination of human milk and formula. Despite this heterogeneity in the study criteria, the benefit in reduction of NEC has been demonstrated consistently in most individual studies as well as pooled estimates from meta-analyses. (8)(9)

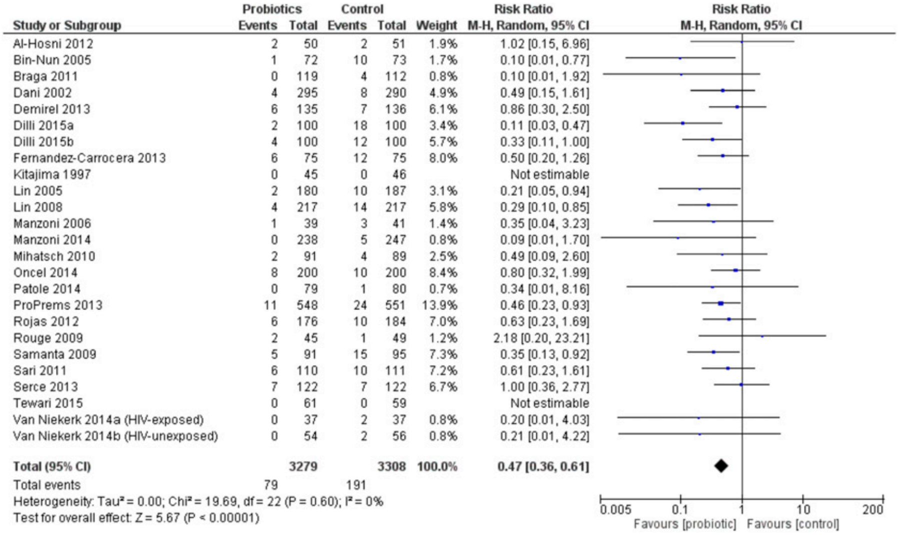
Probiotics for Promoting Feeding Tolerance and Time to Achieve Full Enteral Feeds

In a prospective RCT of probiotics for promoting feeding tolerance in preterm neonates, 104 infants with a birthweight of 750 to 1,499 g were randomized to the probiotic group (n=52) or control group (n=52). (11) There was no statistically significant difference in the primary outcome of time to reach full enteral feeds. (11.2 days vs 12.7 days, P=.4). Findings from the Cochrane review and meta-analysis by AlFaleh and Anabrees revealed that the time to full enteral feeds was lower by 1.32 days (95% CI 1.48-1.17) in the probiotic group compared to the control group. (9) The studies included were of adequate methodologic quality but were significantly heterogeneous with respect to the type of probiotic used, duration of probiotic supplementation, and timing of initiation. While this difference was statistically significant, the effect size may not be significant clinically. In another meta-analysis of 5 studies, exclusively human milk-fed preterm infants receiving probiotic supplementation reached full enteral feeds 3 days sooner than did the control group receiving exclusive human milk feeds without probiotic supplementation. (12) The findings of this study are particularly important because infants in both the study and control groups received an exclusive diet of human milk in contrast to previous studies that included both human milk and formula feeds.

In summary, probiotic supplementation has been shown to decrease time to full enteral feeds among infants fed an exclusive human milk diet. The benefits attributable to probiotic supplementation were in addition to the benefits of human milk diet alone, relative to formula.

Probiotics for Preventing Late-Onset Bacterial and Fungal Sepsis

Preterm infants are predisposed to sepsis because of their immature immune system and immature skin mucosal



Study or Subgroup	Probiotics Events	Probiotics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Hosni 2012	2	50	2	51	1.9%	1.02 [0.15, 6.96]
Bin-Nun 2005	1	72	10	73	1.7%	0.10 [0.01, 0.77]
Braga 2011	0	119	4	112	0.8%	0.10 [0.01, 1.92]
Dani 2002	4	295	8	290	4.9%	0.49 [0.15, 1.61]
Demirel 2013	6	135	7	136	6.1%	0.86 [0.30, 2.50]
Dilli 2015a	2	100	18	100	3.4%	0.11 [0.03, 0.47]
Dilli 2015b	4	100	12	100	5.7%	0.33 [0.11, 1.00]
Fernandez-Carrocera 2013	6	75	12	75	8.0%	0.50 [0.20, 1.26]
Kitajima 1997	0	45	0	46		Not estimable
Lin 2005	2	180	10	187	3.1%	0.21 [0.05, 0.94]
Lin 2008	4	217	14	217	5.8%	0.29 [0.10, 0.85]
Manzoni 2006	1	39	3	41	1.4%	0.35 [0.04, 3.23]
Manzoni 2014	0	238	5	247	0.8%	0.09 [0.01, 1.70]
Mihatsch 2010	2	91	4	89	2.5%	0.49 [0.09, 2.60]
Oncel 2014	8	200	10	200	8.4%	0.80 [0.32, 1.99]
Patole 2014	0	79	1	80	0.7%	0.34 [0.01, 8.16]
ProPrems 2013	11	548	24	551	13.9%	0.46 [0.23, 0.93]
Rojas 2012	6	176	10	184	7.0%	0.63 [0.23, 1.69]
Rouge 2009	2	45	1	49	1.2%	2.18 [0.20, 23.21]
Samanta 2009	5	91	15	95	7.3%	0.35 [0.13, 0.92]
Sari 2011	6	110	10	111	7.2%	0.61 [0.23, 1.61]
Serce 2013	7	122	7	122	6.7%	1.00 [0.36, 2.77]
Tewari 2015	0	61	0	59		Not estimable
Van Niekerk 2014a (HIV-exposed)	0	37	2	37	0.8%	0.20 [0.01, 4.03]
Van Niekerk 2014b (HIV-unexposed)	0	54	2	56	0.8%	0.21 [0.01, 4.22]
Total (95% CI)		**3279**		**3308**	**100.0%**	**0.47 [0.36, 0.61]**
Total events	79		191			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 19.69$, df = 22 (P = 0.60); $I^2 = 0\%$

Test for overall effect: Z = 5.67 (P < 0.00001)

Figure. Forest plot showing effect of probiotics on necrotizing enterocolitis in very-low-birthweight infants (adapted with permission from Sawh et al [8]).

barrier. In addition, risk factors such as the use of invasive catheters, delayed enteral feeding, lack of human milk, prolonged parenteral nutrition, underlying morbidities, and prolonged hospitalization contribute to this increased risk for sepsis. Furthermore, the establishment of normal gut microbiota may be disrupted by exposure to antibiotics, delayed enteral feeding and lack of exposure to mother's milk. Probiotics are thought to modulate and improve gut barrier and immune function and help reduce the risk of late-onset sepsis.

The evidence that probiotics may reduce late-onset sepsis is controversial. In several meta-analyses, the pooled estimates did not show a reduction in late-onset sepsis in the probiotics group compared with the control group in VLBW infants. (8)(9)(13)(14) However, other meta-analyses have reported a significant reduction in late-onset sepsis in the probiotic group in the LBW and VLBW category, but not in the ELBW category. (15)(16)

The incidence of invasive fungal infections ranges from 2% to 4% in VLBW infants and up to 4% to 16% in ELBW infants. (17) In animal models, probiotics have been shown to reduce fungal colonization and invasive infection by competitive inhibition, augmentation of gut barriers and enhancement of immune function. (18)(19)(20) Other biological mechanisms by which probiotics exert antifungal activity include production of hydrogen peroxide, which antagonizes Candida growth. (21)(22) In a systematic review and meta-analysis of the effect of probiotics on fungal colonization and sepsis, Hu et al reported that prophylactic probiotic supplementation had no effect on invasive fungal sepsis (RR 0.88; 95% CI 0.44-1.78; *P*=.72) but was associated with a lower risk of Candida colonization. (23) In another meta-analysis of probiotics for the prevention of NEC, the risk of fungal sepsis was not affected by probiotic supplementation. (8)

In summary, recent evidence suggests that probiotics may have a beneficial effect in reducing late-onset sepsis in VLBW infants but not in ELBW infants. Probiotics have had no effect on the risk of invasive fungal sepsis.

Probiotics and Neurodevelopmental Outcomes

It has been hypothesized that probiotics may improve neurodevelopmental outcomes by inducing anti-inflammatory cytokines and transforming growth factor β, which may counteract the effect of inflammatory mediators related to the pathogenesis of NEC, sepsis, chronic lung disease, intraventricular hemorrhage, and periventricular leukomalacia. (24)(25)(26)(27)(28) Other proposed mechanisms include improved feeding tolerance, growth, and decreased hospital length of stay.

No studies have specifically evaluated the effect of probiotics on neurodevelopmental outcomes. Secondary analyses of 3 RCTs of probiotics for the prevention of NEC suggest that probiotics have no effect on neurodevelopmental outcomes in preterm infants at 18 to 24 months, but the studies were not powered to assess this outcome. (29)(30)(31) Small sample size and use of a single probiotic strain, as well as complex and multiple factors affecting neurodevelopmental outcomes are cited as reasons for finding no effect or lack of effect of probiotics on neurodevelopmental outcomes in these studies.

Safety of Probiotics

A major concern currently limiting the routine use of probiotics in neonates is the risk of sepsis caused by the supplemented organism in the probiotic product. Preterm neonates are particularly at risk because of their immature immune system and immature gut mucosal barrier function, which can lead to translocation of bacteria and then to sepsis. Although no RCTs or meta-analyses have reported bacteremia or sepsis with the organisms in the probiotic products, this has to be interpreted with caution because many organisms in these products do not grow in aerobic cultures, but instead require anaerobic culture methods. Typically, aerobic blood culture methods are used for neonates, which may underestimate the true incidence of probiotic bacteremia/sepsis. There is also no systematic reporting system for adverse events related to probiotic interventions, making rare adverse events more difficult to assess. (32)

Several published case reports confirm that probiotic-associated bacteremia and sepsis can occur in neonates, infants, and adults. Roy et al reported 7 cases (2 premature neonates and 5 adults) of *Saccharomyces cerevisiae* fungaemia associated with probiotic supplementation containing *Saccharomyces boulardii*. (33) Fluorescent amplified fragment length polymorphism was used to confirm similarities between blood and corresponding probiotic isolates. Esaiassen et al reported *Bifidobacterium longum* bacteremia in 3 of the 290 ELBW neonates who received oral probiotics for the prevention of NEC. (34) Whole-genome sequencing and comparative analysis of nucleotide-level variation methods were used to confirm that the blood culture isolates were identical to the strains used in the probiotic supplement. Zbinden et al reported 3 cases of *B longum*, and Bertelli et al reported 2 cases of *Bifidobacterium infantis* bacteremia associated with prophylactic probiotic supplementation. (35)(36) In some of these patients, signs of early NEC were present at the time of blood culture, and the infants subsequently developed NEC and required surgery. It is conceivable that in those patients, disrupted gut mucosal membranes led to translocation of bacteria, causing sepsis. Kitajima and Hirano reported 4 neonatal cases of *Bifidobacterium breve* bacteremia among approximately 23,000 patients who received the probiotic supplement. (37)

Contamination of probiotic formulations with pathogenic organisms remains a concern. This was validated in 2015 when an infant died of gastrointestinal mucormycosis after receiving a probiotic supplement found to be contaminated with *Rhizopus oryzae,* which was also isolated from his intestines. (38) Another source of concern in the United States is that most available probiotics are produced and regulated as food supplements rather than pharmaceutical products. (7)

Additional safety concerns center around altered immune responses, development and transfer of antimicrobial resistance, and allergic sensitization. Strain-specific alterations in immune responses by Th1 cells, Th2 cells, enterocytes secreting cytokines, and CD8+ cells in the enteric lymph nodes and spleen have been demonstrated. (7) The sequelae of altering the neonatal microbiome (eg, by using broad-spectrum antibiotics) are only now beginning to be understood and appreciated. Presumably, probiotics are altering the immune response in a beneficial way, but some effects may only be seen during large scale and/or long-term use, necessitating ongoing surveillance and reporting. This is particularly important in the smallest premature neonates, who are at the highest risk for adverse effects, but also the group which stands to benefit the most.

It is well known that interspecies transfer of antimicrobial resistance occurs when administering live organisms to patients; therefore, it is logical to be concerned that the administered organisms may be capable of transferring resistance to more virulent pathogens. This transfer, while rare, has been demonstrated and remains a concern. (32)

In summary, sepsis due to probiotic organisms is rare, but information on its occurrence is limited by lack of systematic reporting and a paucity of information on culture methods used to evaluate suspected sepsis. However, probiotic organisms are weakly virulent and antibiotic-sensitive, generally making infection not only rare but also easily treatable.

Which Probiotic Formulation to Use?

While several RCTs show that probiotics reduce mortality and morbidity, the studies used different probiotic strains or combinations. Most existing meta-analyses fail to account for strain-specific effects. To address this issue, Sawh et al performed a network meta-analysis, which showed that only a minority of probiotic strains had a statistically significant effect in reducing NEC and mortality in preterm infants. (8)

Strains or combinations of strains that have been found to significantly reduce the risk of NEC are as follows: *Bifidobacterium lactis; Lactobacillus reuteri; Lactobacillus rhamnosus* GG; the combination of *Bifidobacterium bifidum, B infantis, B longum,* and *Lactobacillus acidophilus;* the combination of *B infantis* and *L acidophilus;* the combination of *B infantis, B lactis Bb-12,* and *Streptococcus thermophilus;* and the combination of *B longum and L rhamnosus GG*. Strains that had the most effect in reducing mortality include *B bifidum, B infantis, B longum, L acidophilus, Lactobacillus casei, Lactobacillus plantarum, L rhamnosus, and S thermophilus.*

In multiple meta-analyses, multispecies probiotic supplementation was associated with a greater reduction in the incidence of NEC and mortality. When comparing species, *Lactobacillus* and *Bifidobacterium* species were found to confer the most benefit. (8)

In summary, if probiotics are used clinically in VLBW infants, a multispecies probiotic supplement containing both *Lactobacillus* and *Bifidobacterium* species would be recommended.

Timing of Initiation, Duration, and Dose

As discussed previously, there was significant heterogeneity in probiotic studies with regard to the timing of initiation, duration of therapy, and the dose used. (8) The most common criteria used for timing of initiation are within 48 hours, after 48 hours, or with the first feed. Duration of therapy ranged from 4 to 6 weeks or until discharge. Probiotic doses typically ranged from 10^8 to 10^{10} colony-forming units per dose. Despite the heterogeneity in study criteria, a statistically significant reduction in NEC and all-cause mortality has been observed consistently. (9)

PREBIOTICS IN NEONATES

Mechanisms of Protection

"Prebiotics" are exogenous products containing substrates promoting colonization by commensal organisms. Although prebiotic use in neonates is still in the investigational stage, they are not new. Human milk contains prebiotic substances called *human milk oligosaccharides*, which arrive at the intestines undigested. In the intestines, these oligosaccharides resemble the carbohydrate-binding structures used by pathogenic organisms and thereby inhibit adhesion and invasion by these enteric pathogens. Beyond inhibiting pathogenic adhesion and serving as a primary carbon source for the commensal *Bifidobacterium* species present in the neonatal intestine, exposure to these compounds stimulates the expression of bacterial genes involved in digestion, thus giving these organisms a competitive advantage over other organisms present in the intestinal lumen. In addition, when probiotic organisms digest the oligosaccharides, they degrade these compounds into short-chain fatty acids. These bacterial byproducts serve as an energy source for intestinal epithelial cells and strengthen the intestinal barrier. (39)

Commercially prepared prebiotic compounds include galacto-oligosaccharides, which are one form of human milk oligosaccharide, and fructo-oligosaccharides, which are derived from vegetables. These exogenously administered products have effects resembling those seen with the prebiotics present in human milk, including stimulation of commensal microbial growth, inhibition of pathogen adherence, and promotion of epithelial cell barrier function. (39)

Summary of the Evidence

Few studies have examined the health effects of the exogenous administration of commercially prepared prebiotics in neonates. One meta-analysis examining prebiotics in preterm neonates included 7 RCTs (n=417). The analysis found that prebiotics are associated with some physiologic changes such as decreased stool pH, stool viscosity, and gastrointestinal transit time. *Bifidobacteria* species growth from stool samples was also increased with the use of prebiotics, but there were no differences in the clinical outcomes of NEC, late-onset sepsis, or time to full enteral feeds. (40) Although life-threatening adverse events have not been identified, intestinal side effects such as altered stool consistency and flatulence occur when these indigestible materials are administered in high doses. (39)

Assessing the effects of probiotics in neonates is challenging because of the various cultures used in clinical trials and in practice, as is the assessment of the efficacy and safety of prebiotic substances. The specific formulation and dose likely alter the activity and safety of the product. For example, lactulose-containing prebiotics promote the growth of *Lactobacillus* species, whereas other oligosaccharide products promote *Bifidobacterium* species. This issue becomes more confounded when considering that many of the beneficial effects of prebiotics are conferred only in the presence of colonization by certain commensal organisms. Infants, for example, who have received or are receiving broad-spectrum antibiotics, may not see the same effects. (40)

SYNBIOTICS IN NEONATES

Similar to prebiotics, the investigations of combination products containing both probiotic cultures and prebiotic substrates, referred to as *synbiotics*, in neonates have been quite limited. The results have been conflicting, but some synergistic effects on the modulation of inflammatory markers have been seen in animal models of NEC. (39)

Three recent clinical trials examined synbiotics in neonates. A single-center RCT in southern India included 220 infants receiving breast milk and showed a decreased incidence in NEC with the administration of a product containing *Lactobacillus*, *Bifidobacterium*, and a fructo-oligosaccharide, compared to placebo. (41) A multicenter RCT in Turkey randomized 400 VLBW infants to a control arm or 1 of 3 study arms that were administered *B lactis,* inulin (a prebiotic oligosaccharide), or both. (42) The incidence of NEC was lower in the probiotic and synbiotic groups, but not the prebiotic group, compared to controls. Other outcomes were improved in all 3 treatment groups as compared to controls. Both probiotics and synbiotics were effective in this trial, but there was no additive effect of a synbiotic compared to probiotics alone. Another RCT in southern India compared 100 infants in a control group with 100 infants receiving a fructo-oligosaccharide as well as *L acidophilus, B longum, B bifidum,* and *S thermophiles* cultures. The infants receiving the multistrain synbiotic product had a decreased incidence and severity of NEC compared to the control group. (43)

CONCLUSIONS

Based on multiple RCTs and meta-analyses, we believe the beneficial effects of probiotics given to VLBW infants for the prevention of NEC and the decrease of all-cause mortality have been established. Nonetheless, the sole "clinical report" published by the American Academy of Pediatrics (AAP) on probiotic use does *not* recommend the routine use of probiotics in this population. (44) The report states that more studies are needed. Moreover, in the 8th edition of *Guidelines for Perinatal Care* (published jointly in 2017 by the AAP and the American College of Obstetricians and Gynecologists), there are no recommendations on the use of probiotics. (45) Therefore, the use of probiotics in this population cannot yet be considered standard of care. More research is needed to assess the risks and benefits of these substances, as well as to examine the most effective dosage, formulation, and duration. If clinicians choose to use probiotics in clinical practice, only formulations previously demonstrated as safe and efficacious by ensuring high degree of quality control should be used.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the immunologic and anti-infective constituents in human milk and their physiologic effects.
- Know the pathophysiology of NEC.

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1. A female infant born at 25 weeks' gestational age is receiving probiotics as part of a protocol for preventing necrotizing enterocolitis. Which of the following is a potential beneficial action of probiotics in the preterm infant's gut?

    A. Decreased production of mucus.
    B. Reduced number and diversity of colonized bacteria.
    C. Increased production of secretory immunoglobulin A.
    D. Slowing of gut motility to facilitate digestive actions.
    E. Promotion of apoptosis of intestinal cells to facilitate cycling of new immune cells along the bowel wall.

2. In considering the use of probiotics in the NICU, your team reviews the literature of clinical trials for the prevention of necrotizing enterocolitis. As of 2016, systematic reviews and meta-analyses have shown the clearest benefit of necrotizing enterocolitis prevention in which population?

    A. Very-low-birthweight infants (birthweight $<$1,500 g).
    B. Extremely low-birthweight infants (birthweight $<$1,000 g).
    C. Recurrence in patients who have already had necrotizing enterocolitis.
    D. Infants with birthweight of 1,500 to 2,500 g.
    E. Infants with abdominal wall defects such as gastroschisis or omphalocele.

3. A newborn preterm male infant who was born at 25 weeks' gestational age is started on small breast milk feedings and probiotics at 1 day of age. Probiotics have clearly shown benefit in preventing which of the following in preterm infants?

    A. Invasive fungal sepsis.
    B. Early-onset sepsis with group B *Streptococcus* infection.
    C. Time to full enteral feedings when infants are fed exclusive human milk diet.
    D. Severe neurodevelopmental delay as assessed at 18 to 24 months.
    E. Severe (grade 3 or 4) intraventricular hemorrhage.

4. In case reports of neonates receiving probiotics, randomized controlled trials have not yet reported bacteremia or sepsis with the organisms in probiotic products. However, some adverse events have been noted. Which of the following adverse events have been reported in neonates receiving probiotics in more than 1 patient?

    A. Severe neutropenia and thrombocytopenia.
    B. Pyloric stenosis.
    C. Necrotizing enterocolitis with associated group B *Streptococcus* bacteremia and sepsis.
    D. *Bifidobacterium longum* bacteremia in preterm infants fed probiotic supplementation having a formulation including that species.
    E. Disseminated multiresistant *Mycobacterium* tuberculosis infection.

5. Studies of probiotics in preterm infants have used multiple combinations of strains. Which of the following species of probiotics have been shown to confer the most benefit in preventing necrotizing enterocolitis?

    A. *Enterococcus* and Candida.
    B. *Streptococcus thermophile* and *Streptococcus agalactiae*.
    C. *Rhizopus* and *Klebsiella*.
    D. *Lactobacillus* and *Bifidobacterium*.
    E. There are no perceptible differences in clinical outcomes based on strain because any formulation appears to confer similar benefit.

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Influences of Feeding on Necrotizing Enterocolitis

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Education Gap

Despite the recognition that enteral feeding and some clinical conditions encountered during the management of prematurity may affect the development of necrotizing enterocolitis (NEC) in premature neonates, there is still significant variation in practice. Clinicians should be aware of the current evidence regarding feeding and the development of NEC in premature neonates, specifically relating to the use of breast milk, feeding when a patent ductus arteriosus is present and during its treatment, as well as the potential association of NEC with anemia and red blood cell transfusions.

Abstract

Necrotizing enterocolitis (NEC) remains one of the leading complications of prematurity with an incidence of 5% to 13% and a mortality of up to 30%. Its occurrence is inversely related to gestational age, with the most premature neonates being at highest risk. Despite numerous studies assessing risk factors, the most commonly observed associations remain prematurity and enteral feeding. Furthermore, studies have pointed to receipt of breast milk as a protective factor in decreasing the risk of NEC and formula feeding as potentially increasing the risk. Other potential risk factors and associations in the premature infant include lack of antenatal steroids, receipt of prolonged courses of postnatal antibiotics, presence of anemia, receipt of packed red blood cell transfusions, and presence of a patent ductus arteriosus. Despite the recognition that NEC remains a serious complication of prematurity, there is still no specific prescription for its prevention. Given that enteral feeding is one of the most commonly observed risk factors for the development of NEC, wide variation exists in the enteral feeding recommendations and practices for premature infants. Feeding practices that may contribute to NEC, which remain variable in practice, include feeding strategies used in the presence of a hemodynamically significant patent ductus arteriosus and feeding during packed red blood cell transfusions. Use of breast milk (mother's own milk or donor milk) is recognized as one of the mainstays of NEC prevention. This article explores multiple influences of feeding on the development of NEC.

Objectives After completing this article, readers should be able to:

1. Recognize the impact of breast milk on the occurrence of necrotizing enterocolitis (NEC).

AUTHOR DISCLOSURE Drs Thompson-Branch and Havranek have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CI	confidence interval
GI	gastrointestinal
NEC	necrotizing enterocolitis
NIRS	near-infrared spectroscopy
NPO	nil per os
OR	odds ratio
PDA	patent ductus arteriosus
PRBC	packed red blood cell
RCT	randomized controlled trial
RR	risk ratio
SMA	superior mesenteric artery
TANEC	transfusion-associated NEC
VLBW	very low birthweight

2. Describe the association between a patent ductus arteriosus, its pharmacologic treatment, and the development of NEC.
3. Explain the possible contribution of anemia, receipt of red blood cell transfusion, and the impact of feeding on NEC.

INTRODUCTION

Necrotizing enterocolitis (NEC) remains one of the leading complications of prematurity, affecting between 5% and 13% of premature infants and is the most common gastrointestinal (GI) emergency in this population. Its occurrence is inversely related to gestational age with the most premature neonates being at highest risk. (1) The most commonly found associations remain prematurity and enteral feeding. Breast milk appears to confer protection from NEC and formula feeding potentially increases the risk. Other potential risk factors and associations include lack of antenatal steroids, receipt of prolonged courses of postnatal antibiotics without bacteremia, presence of anemia, receipt of packed red blood cell (PRBC) transfusions, and presence of a patent ductus arteriosus (PDA). (2)(3)(4)(5)(6)(7)(8)(9)

NEC remains a serious complication of prematurity; however, there is still no specific prescription for its prevention. Although enteral feeding is one of the most commonly observed risk factors for the development of NEC, wide variation still exists in the enteral feeding recommendations and practices for premature infants. This article briefly discusses the pathogenesis of NEC and explores the evidence behind the influences of feeding on the development of NEC.

PATHOGENESIS

The origin of NEC is multifactorial, with intestinal immaturity at its center and genetic susceptibility, inflammation, the altered microbiome of the premature gut, and hemodynamic instability being additional contributory factors. (10) While the pathogenesis of NEC is still being explored, at its core, it is thought to arise from the premature state of the gut. Prematurity portends an impairment of intestinal repair mechanisms, limited mucin production, and other forms of gut protection, leading to a more porous intestinal epithelium. (11) Activation of toll-like receptor 4 and impaired innate immunity lead to a proinflammatory state. These immune factors are genetically determined and may increase or decrease the risk of NEC. (12) A lack of microbial diversity and colonization with predominantly pathogenic bacteria are also established in infants at higher risk of NEC especially when enteral feedings using formula are introduced. (13)(14) The effects of low blood flow states and transient hypoxemia likely cause ischemic injury to an already predisposed gut. Impaired gut motility leads to bacterial stasis, with subsequent bacterial translocation across a leaky, inflamed, and ischemic intestinal epithelium contributing to the pathogenesis of the disorder. (10)(15)

The most commonly described risk factors for NEC are extreme prematurity and enteral feeding. Numerous studies have pointed to the receipt of breast milk as a protective factor in decreasing the risk of NEC. (16) Other potential risk factors and associations include lack of antenatal steroids, receipt of prolonged antibiotics, presence of anemia, receipt of PRBC transfusions, presence of a hemodynamically significant PDA and enteral feeding during its treatment, and other low blood flow states. (2)(3)(4)(5)(6)(7)(8)(9)

DIAGNOSIS AND MANAGEMENT

Symptoms in patients with NEC may include nonspecific metabolic derangements or symptoms specific to the GI tract. GI signs and symptoms may include bilious emesis, hematochezia, abdominal distention, abdominal tenderness, and discolored abdomen. Other signs and symptoms may include lethargy or irritability, cardiorespiratory derangements (apnea, bradycardic episodes, oxygen desaturation, need for increased respiratory support, respiratory acidosis, hypotension), hematologic abnormalities (thrombocytopenia, disseminated intravascular coagulopathy, low or elevated white blood cell count), renal failure (associated electrolyte abnormalities such as hyponatremia, hyperkalemia), metabolic acidosis, bacteremia, and sepsis syndrome.

The hallmark of diagnosis is clinical symptoms coupled with the presence of pneumatosis on abdominal radiography. Abdominal distention, presence of a sentinel intestinal loop, portal venous gas, a paucity of gas, gasless abdomen, and the presence of pneumoperitoneum may also be observed radiographically. The modified Bell staging criteria are used to delineate 3 stages of NEC and the associated signs and symptoms. (17) Because symptoms of stage I NEC can be nonspecific and short-lived, many studies use NEC stage II or higher as their definition of the disorder.

Management includes bowel rest with intestinal decompression, broad-spectrum antibiotics, and supportive care for multisystem organ failure as needed. Serial radiographs are used to monitor for progression of disease. Surgical treatment is warranted in case of a worsening clinical picture or if pneumoperitoneum is noted on abdominal radiography. Approximately 30% of affected neonates require surgical management. NEC has a mortality of up to 30%, with the highest mortality seen in infants who receive surgical management. (15) Short gut, cholestatic liver failure, prolonged hospital stays with increased medical costs, and more significant neurodevelopmental impairment are additional concerning outcomes. (18)(19)

IMPACT OF GENERAL FEEDING PRACTICES ON THE DEVELOPMENT OF NEC

Though enteral feeding is one of the most commonly observed risk factors for the development of NEC, wide variation exists in enteral feeding recommendations and practices for premature infants. (20)(21) Once relative stability has been achieved after the birth of a premature infant, enteral feedings are initiated. Availability and use of an institutional feeding protocol addressing timing of initiation of enteral feedings, use of trophic feedings, use of breast milk versus preterm formula, fortification of feedings, use of continuous versus bolus feedings, and the pace of feeding advancement are some of the variations in practice that are observed and whose evidence is examined further in this article.

Standardized Feeding Protocols

Studies have shown a reduction in NEC rates with the use of institution-specific standardized feeding regimens. A 2017 meta-analysis by Jasani and Patole (22) evaluated 15 observational studies spanning the years 1978 to 2016 and involved 18,160 premature neonates of less than 37 weeks' gestational age. A 78% reduction in NEC stage II or higher was observed with the use of a standardized feeding regimen (risk ratio [RR] 0.22; P=.0001; 95% confidence interval [CI] 0.13-0.36). (22) To account for possible practice changes over time, 2 different epochs were compared, 1978 to 2004 and 2004 to 2016. The results were still significant in both periods, indicating that the use of standardized feeding regimens decreased NEC rates.

Trophic Feedings/Minimal Enteral Nutrition

It was hypothesized that using a strategy of minimal enteral nutrition or trophic feedings for the first few days of enteral feeding shortly after birth for premature infants, compared with keeping the infant nil per os (NPO) would allow the premature gut to be "primed," promoting intestinal maturation and hence a reduction in the incidence of NEC. A Cochrane review in 2013 analyzed 9 trials with 754 study subjects in which trophic feedings with milk volumes up to 24 mL/kg per day were initiated before 96 hours' postnatal age and continued until at least 1 week after birth. (23) There was no statistically significant effect on the incidence of NEC (RR 1.07; 95% CI 0.67-1.70). (23) It is possible that, despite the lack of a statistical effect indicating a decreased incidence of NEC when studies were pooled, there may be sicker, more premature, and more vulnerable populations of premature infants who may benefit from the use of trophic feedings or minimal enteral nutrition.

Delayed versus Early Advancement of Enteral Feedings

It has been postulated that delaying the progressive advancement of feedings for some days after initiation of enteral feedings could reduce the likelihood of NEC. A Cochrane review in 2014 addressed this question, seeking to compare infants who had early (days 1-4 after birth) versus delayed (days 5-7 after birth) advancements of their enteral feedings. (24) Overall, 9 studies were included in the meta-analysis, with 1,106 subjects who were very preterm (<32 weeks' gestational age at birth) or very low birthweight (VLBW; <1,500 g). The NEC analysis included 8 trials with 1,092 subjects. A statistically significant effect on the risk of NEC was not found (RR 0.93; 95% CI 0.64-1.34). This would suggest that it is not beneficial to delay advancement of enteral feedings past 4 days after birth, because it does not portend a reduction in NEC risk. It was noted that most of the study subjects were not extremely premature (few were born at <28 weeks' gestational age); hence, it is unclear that these results are generalizable to this cohort of premature infants who would have the highest risk of NEC. (24)

Slow versus Fast Feeding Advancement

It is hypothesized that advancing enteral feedings in premature neonates at a pace greater than that considered trophic, that is, greater than 20 mL/kg per day, may increase the risk of NEC in premature neonates. In a 2017 Cochrane review, slow (<24 mL/kg per day) versus faster (30-40 mL/kg per day) enteral feeding advancement rate did not result in a statistically significant difference in NEC for very preterm or very low birthweight infants. (25) Included in the meta-analyses were 10 randomized controlled trials (RCTs) with 3,753 subjects (NEC RR 1.07; 95% CI 0.83-1.39). In this meta-analysis, approximately one-third of subjects were extremely premature or extremely low birthweight (<1,000 g), potentially limiting the generalizability of the results to this population subset at the highest risk of NEC. (25)

Breast Milk (Mother's Own Milk and Donor Milk) versus Formula

The benefits of breast milk for premature infants are many and include a reduction in the incidence of NEC, lower rates of retinopathy of prematurity, reduced episodes of late-onset sepsis, improved neurodevelopmental outcomes, and fewer hospital readmission rates during the year after discharge from the NICU. (26)(27)(28)(29)(30) Reduction in rates of bronchopulmonary dysplasia has been demonstrated less consistently. (26)(27)(28)(29)(30) These benefits are observed even with nonexclusive breast milk use. Breast milk contains many protective factors, including bactericidal, immunologic, antioxidant, and anti-inflammatory properties. (31) Maternal white blood cells, lysozymes, secretory immunoglobulin A, various growth factors, lactoferrin, oligosaccharides, and commensal bacteria are among its protective factors. (32)(33)

Although breast milk use has multiple desirable benefits, including reduction in some of the catastrophic comorbidities experienced with prematurity, without fortification, it can be suboptimal for growth and nutritional balance for the rapidly growing premature infant. There are no studies that directly compare, in randomized fashion, mother's own milk to formula. However, one study evaluating a prospective cohort of premature infants grouped by those who received more than 50% of breast milk in the first 14 days of age versus those who received less than 50% of breast milk showed a reduction in NEC. In the high proportion of breast milk (>50%), NEC occurred at a rate of 3.2% versus 10.6% in the low proportion of breast milk (odd ratio [OR] 0.17; 95% CI 0.04-0.68). (34) In an analysis of 1,272 infants enrolled in the National Institute of Child Health and Human Development glutamine study, increasing human milk intake was associated with a decreasing risk of NEC. Of these infants, 13.6% developed NEC after 14 days of age. (35) For each 10% increase in the amount of milk received, risk for NEC (or death) decreased by 0.83 (95% CI 0.72-0.96). (35) It is still unclear, however, what the threshold is for volume or proportion of milk to which a premature neonate would need to be exposed in order to benefit from its use, if that infant is unable to be exclusively fed breast milk.

When exclusive breast milk use is desired and mother's own milk is unavailable, a donor milk option is available, albeit at a significant expense. The processing of donor milk may reduce some of the protective properties. In addition, donor milk is typically pooled from mothers of larger or full-term infants whose milk composition is different from that of the mother of a premature infant. (27) It is, however, recognized that the use of donor milk also reduces the risk of NEC when compared with formula. In a 2014 Cochrane review comparing donor milk to formula, 9 trials were included, with 1,070 subjects. (16) A significant increase was noted in the risk of NEC in infants receiving formula (OR 2.77; 95% CI 1.40-5.46). (16) In a 2016 study by Chowning et al, a retrospective chart review was undertaken of 550 VLBW infants who received some proportion of mother's own milk and donor milk. (36) The results indicated that receipt of human milk, mother's own or donor, for more than or equal to 50% of hospital days was associated with a statistically significant reduction in NEC, from 13.5% to 3.4% ($P<.001$). (36) While donor milk presents a significant opportunity for reduction in rates of NEC, concern exists regarding suboptimal growth. Hence, attention to optimal fortification is warranted. (27)

Fortification

Although breast milk is seen as the most optimal nutrition for premature neonates and is associated with reduced rates of NEC, to meet the needs of the growing premature infant, fortification with protein or fat as well as micronutrients is needed. This need is even more pressing when donor milk is used. (27) It was thought that with the addition of fortification products and other medications to breast milk, there is an increase in osmolality that may warrant caution. On average, the osmolality of fortified breast milk (without protein additive) is similar to that of preterm formula. (37) It is common practice to wait for establishment of at least half of the daily enteral breast milk volume before fortifying. However, given the link between achieving normal or close to normal growth patterns and improved outcomes related to prematurity, it may be beneficial to fortify breast milk feedings earlier. Tillman and colleagues performed a retrospective pre-post study comparing 53 premature infants of less than 31 weeks' gestational age whose feedings were fortified at first feed and 42 others fortified between 50 and 100 mL/kg per day of breast milk feedings. (38) There was no observed effect on NEC incidence. (38) Shah and colleagues performed a randomized study assessing whether early (20 mL/kg per day) versus delayed (100 mL/kg per day) fortification affected feeding tolerance and time to full feedings; NEC was not noted to be different between the 2 groups. (39)

Bovine versus Human Milk Fortifiers

Despite the reduction in NEC that breast milk offers, its use alone may lead to lower postnatal growth rates compared with preterm cow milk formula of equivalent caloric density, necessitating the use of fortifier products. (27) There has been increased emphasis on minimizing cow milk in the diet of premature infants when possible, including the products available for fortification. An all-human milk diet, including fortifier products, is associated with the lowest risk of NEC. In a study by Sullivan et al, 207 premature infants fed human milk were randomized to 3 groups: 2 groups received pasteurized donor human milk-based human milk fortifier when mother's own milk or donor milk feedings reached 100 and 40 mL/kg per day, respectively, and the third group received bovine-based human milk fortifier and preterm formula if mother's milk was unavailable. (40) They found the groups that received exclusive human milk diets including fortification had significantly lower rates of NEC (P=.02), and "surgical NEC" (P=.007). (40) Other studies have supported this conclusion as well. (30)(41)(42) There is also a suggestion that nonacidified liquid human milk fortifier added to human milk may offer the greatest reduction in NEC. (43)

Continuous versus Bolus Feedings

It has been purported that feedings may be better tolerated by premature infants if administered in a continuous fashion. However, a Cochrane review in 2011, evaluating 7 trials with 511 VLBW subjects, showed no difference in NEC when continuous oro- or nasogastric feedings were compared with bolus feedings given every 2 or 3 hours. (44)

THE INFLUENCE OF A PATENT DUCTUS ARTERIOSUS ON NEC

In utero, a PDA is responsible for the shunting of oxygenated blood into the systemic circulation. Postnatally, for approximately 30% of preterm infants (higher rates with earlier gestational age) there is delayed spontaneous closure of this shunt, leading to increased pulmonary blood flow after pulmonary pressures drop, and "ductal steal" with decreased systemic blood flow. (8) This phenomenon can lead to impaired perfusion of distal organs, including the gut, which has been purported to cause feeding intolerance and possibly NEC. (45)(46)(47) The effects of a hemodynamically significant PDA on superior mesenteric artery (SMA) blood flow have been examined, with some correlation seen in Doppler blood flow velocity parameters. (47)(48) SMA blood flow response has been noted to be blunted in the presence of a PDA in baboons and human infants. (49)(50)

Increasingly conservative management is being practiced for stable premature infants. (51) In cases of a symptomatic PDA, treatment options for closure include cyclooxygenase inhibitors indomethacin and ibuprofen, and more recently, acetaminophen, as well as surgical ligation for symptomatic persistent PDAs. (52)(53)(54) Indomethacin has been associated with vasoconstrictive phenomena affecting distal organs and causing spontaneous intestinal perforation, and in some cases, increased risk of NEC as well as renal insufficiency. (52)

In a large systematic review published in 2018, Mitra et al compared various pharmacologic treatments for PDA closure. (55) They evaluated 68 randomized clinical trials with 4,802 premature and/or low-birthweight subjects. Although the PDA closure rate was 67.4% and was highest with high-dose oral ibuprofen, in a comparison of placebo with all other medical treatment, no differences in NEC were observed. (55)

Indomethacin can be administered via a prolonged or shorter course. However, based on a systematic review done in 2007 evaluating 5 studies with 431 study subjects, the prolonged course (>4 doses) of indomethacin was associated with increased NEC risk (RR 1.87; 95% CI 1.07-3.27). (56) Ibuprofen is associated with less vasoconstrictive effects with a better GI and renal side effect profile, yet has comparable PDA closure rates. (52) A Cochrane review done in 2015 evaluating 33 studies with 2,290 subjects compared treatment of PDA in premature, low-birthweight neonates using indomethacin, ibuprofen, placebo, or no treatment. (57) Results indicated that ibuprofen was just as effective as indomethacin for PDA closure. However, the risk of developing NEC was reduced for ibuprofen (16 studies, 948 infants; RR 0.64; 95% CI 0.45-0.93). (57) In addition, Doppler blood flow studies show less vasoconstrictive effects on mesenteric and renal artery with ibuprofen compared with indomethacin. (58) Acetaminophen has been studied as a relatively newer therapy for PDA closure. In a Cochrane review of 8 randomized studies including 916 infants, acetaminophen was found to be as effective as ibuprofen, but the evidence was considered to be of low quality to assess the effectiveness in comparison with indomethacin. (54) However, concern exists for neurodevelopment impairment, with autism or autism spectrum disorders suggested with pre- and postnatal exposure to the drug. (54) Additional studies with long-term follow-up are ongoing.

FEEDING IN THE PRESENCE OF A PERSISTENT PDA AND ITS PHARMACOLOGIC TREATMENT

Because of the vasoconstrictive effects of pharmacologic treatment of a PDA and its potential increased risk of

NEC, clinicians sometimes reduce or terminate enteral feedings when a hemodynamically significant PDA is discovered; this practice may vary regionally. (59) Jhaveri et al reported a survey on US- and non-US-based neonatologists regarding their beliefs about whether feedings should be withheld when a persistent PDA is suspected. (59) Results indicated that if neonatologists felt that they had to stop feedings, then they would ligate a PDA irrespective of the need for respiratory support. Of the US neonatologists surveyed, 70% believed that enteral feedings need to be stopped in the presence of a hemodynamically significant PDA. (59) Meanwhile, 70% of non-US neonatologists believed that enteral feedings should continue in the presence of a hemodynamically significant PDA. (59) There are few randomized studies to guide practice.

Bellander et al performed a retrospective review to address whether feeding with breast milk within a few hours after birth in neonates who were less than or equal to 29 weeks' gestational age at birth and ultimately received indomethacin treatment for a PDA led to increased GI risks. (60) There was no difference in the outcome of NEC between the 2 groups. Clyman et al assessed enteral feeding during indomethacin and ibuprofen treatment of a PDA. (61) One hundred seventy-seven preterm infants of more than 31 weeks' gestational age at birth were randomized to trophic feedings versus NPO. The results indicated that the time to achievement of 120 mL/kg per day feedings was less in the trophic feeding group and there was no increase in NEC. (61) A retrospective cohort study by Louis et al in 2016 assessed the risk of NEC when neonates were divided into 3 feeding groups: (NPO [n=229], <60 mL/kg per day [n=142], and >60 mL/kg per day [n=44]) and who received indomethacin for PDA treatment. (62) No difference in the primary outcome of NEC was observed. (62)

TRANSFUSION-ASSOCIATED NEC

Recently, clinicians have expressed concern about transfusion-associated NEC (TANEC), also called *transfusion-related acute gut injury* or *transfusion-related NEC*. This condition is most commonly defined as NEC occurring within 48 hours of receiving a PRBC transfusion. (4)(63)(64) Its etiology has been said to be multifactorial and may relate to an increase in proinflammatory cytokines seen after PRBC transfusion in neonates, alterations in vascular adaptability after transfusion (seen on near-infrared spectroscopy [NIRS] as higher intestinal tissue oxygen saturation as well as altered blood flow velocity noted on Doppler studies) and reperfusion injury related to sudden correction of anemia in poorly perfused and oxygenated intestinal tissues. (65)(66)(67)(68) Singh et al, in their retrospective case-control study, found that both a lower hematocrit and PRBC transfusion increased the likelihood of NEC. (3)

Despite the presence of observational studies linking the temporal receipt of PRBC to the development of NEC, there is still strong debate about whether TANEC is an actual pathologic entity, that is, is the receipt of PRBCs simply an association or is it causative in some cases of NEC? Included in this debate are theories as to whether the degree of anemia before transfusion is the factor that predisposes patients to TANEC. (5)(63)(69) Hay et al (70) performed a systematic review and graded the quality of the available evidence around the TANEC phenomenon. Most of the studies evaluated were observational (n=23) with only 3 randomized studies addressing the allocation of PRBC transfusions. When the definition of NEC occurring within 48 hours of PRBC transfusion was used, the results did not show a statistically significant association of NEC with PRBC transfusion. (70) Similarly, Garg et al performed a meta-analysis of 17 observational studies and did not find an independent association between PRBC transfusion and NEC. (71)

FEEDING DURING PRBC TRANSFUSION

Because of the possible association of PRBC transfusion and development of NEC, some neonatal units have developed transfusion guidelines based on consensus within their unit regarding whether to feed during PRBC transfusions, and for how long a duration to maintain NPO, as well as changes in volume of feedings upon reinitiation. Withholding feedings during PRBC transfusion for the smallest and youngest premature infants may mean need for intravenous access, initiation of intravenous fluids, and possible prolongation of the time to acquire full enteral feedings. Despite the adoption of peritransfusion feeding cessation guidelines by many centers in varying forms, there is limited evidence from randomized trials to guide hemoglobin or hematocrit cutoffs as well as the duration of time for which to withhold enteral feedings to protect from TANEC.

In 2014, DeRienzo and colleagues published a retrospective cohort study of VLBW infants comparing outcomes before and after institution of a peritransfusion feeding protocol. (69) The incidence of NEC decreased from 12% to 7% in the pre- to postprotocol interval (P=.01). However, the incidence of TANEC (NEC within 48 hours of a PRBC transfusion) remained the same in both intervals, 41% of the total number of NEC cases. The risk of TANEC was higher with lower pretransfusion hematocrit (OR 0.87; 95% CI 0.79-0.95). (69)

Marin and colleagues published a study in 2014 in which they assessed mesenteric tissue oxygenation measured by NIRS in preterm infants less than 33 weeks' gestation at birth, categorized into 2 groups: those who were fed (n=9) during PRBC transfusion and those not fed (n=8). (72) Mesenteric oxygenation was assessed for up to 48 hours after PRBC transfusion. Upon resuming feedings, they found lower postprandial mesenteric oxygenation trends in infants fed during transfusions, compared with positive trends in those who were not fed during the transfusion interval. This could indicate a risk of mesenteric ischemia that may potentiate the development of TANEC in infants fed during PRBC transfusions. (72)

Pitzele and colleagues explored whether postprandial SMA blood flow velocity would be affected in neonates who were all fed during PRBC transfusion. (73) Infants were VLBW preterm infants, older than 14 days, who received transfusions while being bolus fed every 3 hours. Pre- and postprandial SMA blood flow velocity was assessed, as well as immediately before and after transfusion and at 24 and 48 hours after transfusion. They found that SMA blood flow velocities were blunted immediately after the transfusion and then normalized at 24 hours after transfusion, suggesting that there may be a period of increased risk of ischemia after PRBC transfusion that may potentiate the risk of TANEC. (73) Importantly, they observed normal postprandial responses in the anemia, in the pretransfusion period. (73)

A systematic review undertaken by Jasani et al in 2017 sought to review the effect of withholding feedings during PRBC transfusion on TANEC. (74) In this review, TANEC was defined as NEC stage II or higher occurring within 48 to 72 hours after a PRBC transfusion. No RCTs were available for inclusion in the review; 7 nonrandomized studies with 7,492 study subjects were included. The results indicated that the practice of withholding feedings during PRBC transfusion significantly reduced the incidence of TANEC (RR 0.47; P=.005; 95% CI 0.28-0.80). Of note, the feeding protocols used in the included study varied in the amount of time feedings were withheld before transfusion, the total NPO duration, when feedings were restarted, and if feedings were restarted at lower than prior volumes, how fast they were advanced. (74)

DISCUSSION

A 2006 survey assessing nutrition practices in the NICU for 3 different birthweight categories was undertaken by Hans et al to determine how current nutrition practice intentions for preterm infants compare with published recommendations and previous feeding practices. Of the invited participants, 23% responded (N=176). (21) Breast milk was the most common first enteral feeding in all birthweight categories. Enteral feedings were initiated earlier and advanced faster than in the past, especially for infants weighing less than 1,000 g at birth. Even though data support the safety of more rapid feeding advancement, more than 80% of surveyed NICUs had slow feeding advancements of 10 to 20 mL/kg per day across all weight categories. (21) This study highlights that evidence and practice sometimes are not concordant. Those charged with the care of premature infants often do not have strong experimental evidence from RCTs by which to guide management, and instead have to weigh and interpret observational or retrospective data to inform our practice. As such, this leads to significant variability in management for common complications of prematurity. One such common issue faced by premature infants is NEC, the most common GI illness in this population. Although prematurity and enteral feeding are the most common risk factors for NEC, the use of breast milk, even if not exclusive and including donor milk, is highly associated with conferring protection from NEC. However, a host of other variables that may influence the risk of NEC come into play, including the timing of initiation of feedings, use of trophic feedings or minimal enteral nutrition, pace and rate of progressive feed advancement, timing of initiation of enteral feed fortification, and continuous versus bolus feedings. Another clinical issue affecting premature neonates is the presence of a PDA which, if hemodynamically significant, is purported to be a risk factor for NEC. While the trend is toward more conservative management for patients with a PDA, challenges for some still include whether to feed with a PDA. In addition, if a PDA is being treated with cyclooxygenase inhibitors, given their vasoconstrictive properties and effect on mesenteric vessels, is there risk of NEC if feeding occurs during treatment? Another common condition encountered is anemia of prematurity. Its treatment with a PRBC transfusion has been noted as associated with the development of NEC. This has prompted many NICUs to use feed withholding strategies during transfusion to prevent TANEC, despite the evidence of direct causality being marginal.

The influences of certain aspects of feeding on the development of NEC are supported by observational evidence in many cases. (20)(75) The Table provides a summary of the evidence regarding influences of the discussed feeding factors on NEC. The lack of high-quality evidence still leaves wide variation in feeding practices that may affect NEC, with the exception of strong recommendations for the use of breast milk and standardized feeding regimens. No RCTs have been performed to date to assess the practice of withholding feedings during PRBC transfusion. Although

TABLE. **Influence of Feeding Factors on NEC: Summary of the Evidence**

FEEDING FACTOR	DECREASES NEC	INCREASES NEC	NO/MINIMAL IMPACT ON NEC	UNCLEAR
Standardized feeding regimen	+ (meta-analysis - 15 observational studies)			
Trophic feedings/minimal enteral nutrition			+ (meta-analysis – 9 RCTs)[a]	
Delayed vs early advancement of enteral feedings (5-7 d vs 1-4 d)			+ (meta-analysis - 9 RCTs)[a]	
Slow versus fast feeding advancement <24 mL/kg per day vs 30-40 mL/kg per day)			+ (meta-analysis - 10 RCTs)[a]	
Breast milk (mother's own milk and donor milk)	+ (meta-analysis – 9 RCTs)			
Formula		+ (mix of study types)		
Fortification				
Osmolality			+	
Timing of initiation			+ (mix of study types)	
Human milk-based human milk fortifier vs bovine fortifier	+ (mix of study types)			
Continuous vs bolus feedings			+ (meta-analysis - 7 RCTs)	
PDA				
Feeding with a PDA				+ (regional variation in feeding practices; epidemiologic association from observational data and suggestion of risk by SMA blood flow studies)
Feeding during pharmacologic treatment of a PDA			+ (retrospective studies × 2 and 1 RCT; trophic/minimal enteral feedings; oral ibuprofen associated with less NEC)	
TANEC				
Anemia		+ (observational)		
PRBC transfusion			+ (meta-analysis - 40 observational, 3 RCTs)	
Withholding feedings during PRBC transfusion	+ (meta-analysis - 7 nonrandomized studies)			

NEC=necrotizing enterocolitis; PDA=patent ductus arteriosus; PRBC=packed red blood cells; RCT=randomized controlled trial; SMA=superior mesenteric artery; TANEC=transfusion-associated NEC.

[a] *Overall low proportion of extremely low-birthweight study subjects.*

the available observational data point toward the positive benefit of this practice, this should not yet be considered standard of care. Moreover, the American Academy of Pediatrics has issued no statements or recommendations concerning the practice.

CONCLUSION

Given that enteral feeding is one of the consistently observed risk factors for NEC, neonatologists need to pay close attention to the varying aspects of feeding and how they influence the incidence of the disease. These observations may translate into practice changes despite lack of high-quality experimental evidence to protect the most vulnerable of our pediatric patient population. Of the feeding-related factors that may influence NEC, the evidence regarding the protection that breast milk confers is the most consistently observed along with the use of standardized feeding regimens. We strongly support the future performance of one or more sufficiently powered RCTs to adequately assess whether withholding feedings during PRBC transfusion makes a difference in the incidence of NEC.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the immunologic and anti-infective constituents in human milk and their physiologic effects.
- Know the pathophysiology of NEC.

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The Rapidity of Advancement of Feedings in Premature Infants: Evidence Basis and Current Recommendations

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Education Gaps

1. Extreme prematurity is a state of nutritional emergency that requires careful attention to avoid catabolism.
2. A number of feeding strategies are commonly used in practice that are not based on evidence.

Abstract

It is every neonatologist's aspiration to achieve "optimal postnatal growth" in preterm infants, because nutrition and growth of this population affect long-term neurodevelopmental outcomes. However, despite having this common goal, there are huge variations in the enteral feeding practices of preterm infants across the globe. One such practice is the rate of advancement of enteral feedings; there is no consensus about the optimal approach, even among international nutritional experts. In this review, we aim to provide readers with the rationale for different practices in feeding advancement and summarize the current literature.

Objectives After completing this article, readers should be able to:

1. Recognize the importance of nutritional management of preterm infants and variations in clinical practice.
2. Explain the rationale of varying opinions about the rate of feeding advancement in preterm infants.
3. Describe the current literature about feeding advancement in preterm infants.

AUTHOR DISCLOSURE Drs Garg and Sinha have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ADEPT	Abnormal Doppler Enteral Prescription Trial
CI	confidence interval
IQR	interquartile range
NEC	necrotizing enterocolitis
RCT	randomized controlled trial
RR	relative risk
SIFT	Speed of Increasing Milk Feeds

INTRODUCTION

Preterm birth, in addition to the problems associated with respiratory, cardiovascular, and immune functions, is also a state of nutritional emergency. As the survival rates of extremely preterm infants have improved over the last few decades, the focus has gradually shifted toward not only keeping these infants alive but also providing the optimum nutrition to improve long-term neurodevelopmental outcomes. (1) It is important that evidence-based nutritional practices are adopted in the general management of preterm infants to provide adequate nutrition and reduce nutritional deficits, facilitate brain growth, and minimize neurodevelopmental morbidities. (2)

Necrotizing enterocolitis (NEC) is a common disorder in the preterm neonatal population that is associated with increased mortality and major long-term morbidity. A number of observational studies indicate that the incidence of NEC may be lower in neonatal units where standardized feeding regimens are practiced. (3) The main aim of most feeding strategies is to safely reach full enteral feedings, avoid significant weight loss, maintain adequate growth, and decrease the incidence of NEC. However, even if a neonatal unit adopts a feeding strategy, there are still substantial variations in the routine day-to-day practical aspects of feeding preterm infants as individual clinicians may have differing preferences. (4)(5) One of the most widely accepted and well-studied practices is the use of mother's own breast milk during initial enteral feeding of preterm infants to minimize the risk of NEC. (6)(7) In contrast, clinicians still have not reached a consensus on other preterm feeding practices such as:

- Time to initiate enteral feeding in the extremely preterm infant.
- Initiation of trophic feedings versus complete fasting for the first few days after birth.
- Rate of advancement (increase of enteral volume).
- Timing for introduction of breast milk fortifiers.
- Use of hydrolyzed protein versus standard preterm formula.
- Role of assessing gastric residuals (quantifying and qualifying).
- Use of probiotics.

ENTERAL FEEDING AND RISK OF NEC

The incidence of NEC in preterm infants has been steady over the last few decades, ranging from 3% to 10% with a mortality rate as high as 30%. (8) The pathophysiology is likely multifactorial and outlined in Fig 1. (8) As mentioned earlier, using mother's own milk remains a significant factor in reducing the incidence of NEC; it is also true that NEC is very rare in infants who have never been fed. (9) Most of the feeding interventions that neonatologists adopt aim to encourage rapid achievement of full enteral feedings to improve postnatal growth but this approach may potentially increase the risk for NEC. It is important for the reader to understand that NEC cannot be prevented by a single strategy intervention. However, the provision of a full package of standardized feeding regimens and practices may decrease the frequency of the disorder. One particular strategy may not be practical or feasible in an individual unit depending on the other influencing or confounding factors. In this review, we mainly focus on the consensus and evidence available for the rapidity of advancement of enteral feeding volume in preterm infants.

CURRENT FOCUS ON ENTERAL FEEDING OF PRETERM INFANTS

Over the past several decades, neonatal clinicians have focused their attention on the day-to-day nutritional care of premature infants. Neonatal dietitians or nutritionists are becoming an integral part of the neonatal team. Pharmacists also work in close collaboration with these clinicians to provide the various regimens of parenteral nutrition that ensure an optimal balance of various macro- and micronutrients. This is particularly crucial in the first several days to weeks after birth while enteral feedings are being advanced and when the maintenance of protein, energy, and lipids may potentially translate into better brain growth and accelerated white matter maturation. (10) Various feeding guidelines written by neonatologists aim to achieve full enteral feeding within the first 1 to 2 weeks after birth. This is an attempt by clinicians to rely more on physiologic enteral feeding and less on parenteral nutrition. Promotion of early enteral nutrition could mean fewer days for invasive lines to be in place and reduce the risk of catheter-related sepsis and other complications. In our neonatal unit, we conducted a retrospective observational study to compare short-term nutritional outcomes in infants born at less than 32 weeks' gestational age during 2 periods (1991 and 2009). (11) The clinicians were much more liberal (aggressive) in providing enteral nutrition to the preterm infants in the 2009 cohort, starting feedings earlier by a mean of 5 days (P=.0001). During the later period, birthweight was achieved earlier by a mean of 4 days (P=.005) and the infants were fully orally fed (breast or bottle) earlier by a mean of 9 days (P=.0001). A similar mindset of providing full enteral feedings sooner rather than later has led to a number of trials over the last few years comparing various rates of feeding advancement to assess safety.

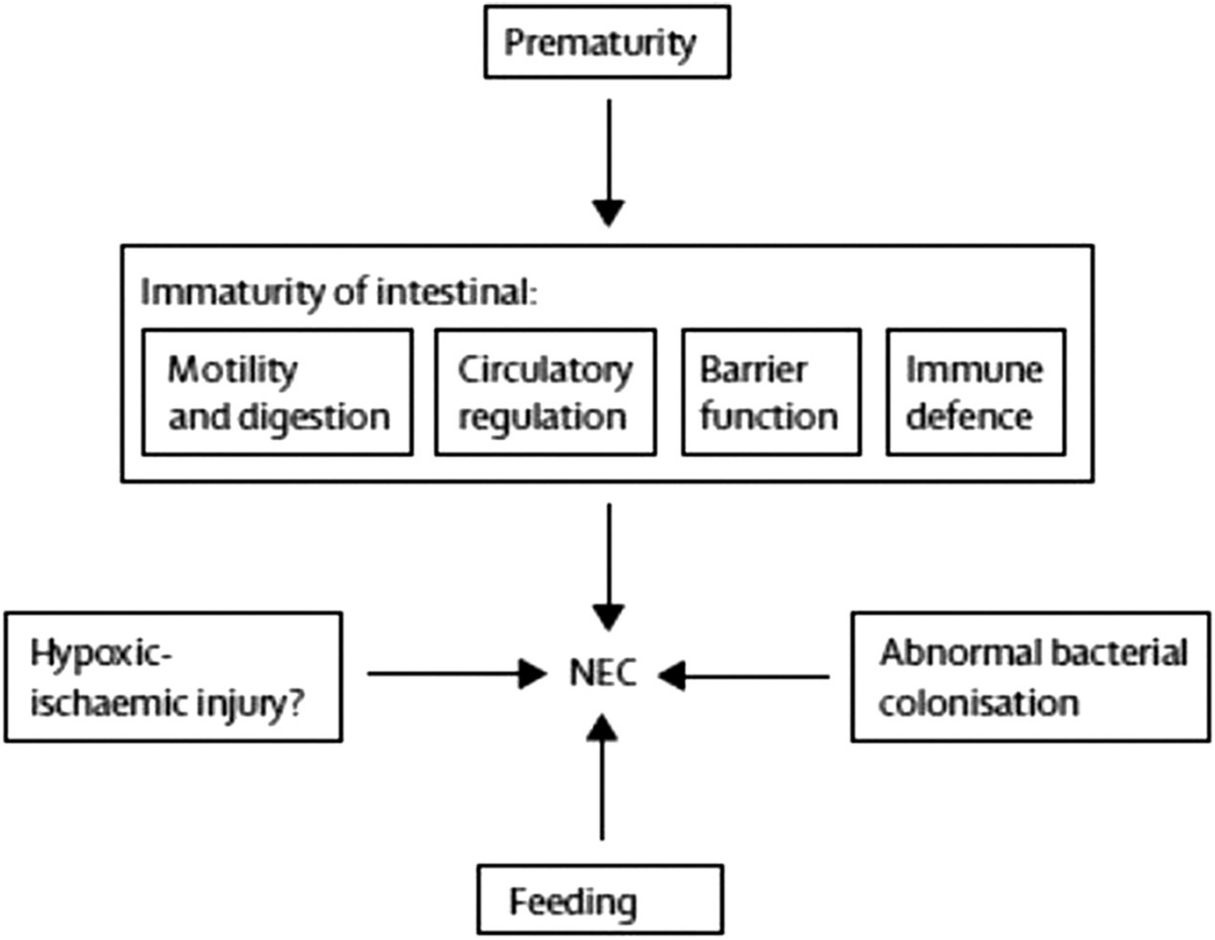


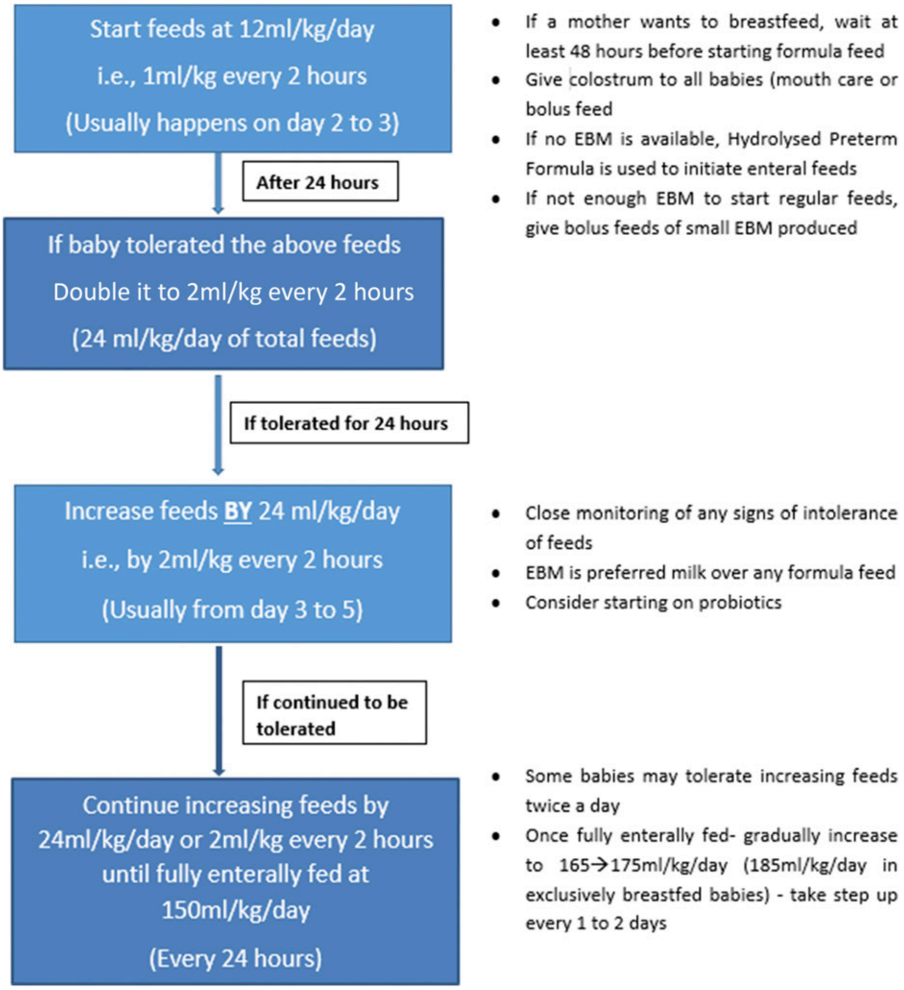
Figure 1. Pathophysiology and interaction of factors responsible for necrotizing enterocolitis. (Reproduced with permission from *Lancet.* 2006;368:1271-1283.)

INITIATION OF ENTERAL FEEDINGS IN PRETERM INFANTS

Most clinicians are in agreement that if the mother's own milk is available, there is no benefit in delaying enteral feedings in hemodynamically stable preterm infants. Initially, preterm infants may only receive a small amount of expressed/pumped colostrum that is placed directly into the child's mouth. As milk production increases, regular interval feedings of a standard minimal volume are given either continuously or as bolus nasogastric feedings, depending on the preferences of individual clinicians or as per local guidelines. This practice is described as *trophic feeding* and the typical volume of milk ranges from 10 to 24 mL/kg per day. Trophic feedings are continued for a variable number of days, as tolerance is established. Once clinicians believe a certain minimal volume is being tolerated, typically after 1 to 3 days, they undertake advancement in volume.

ADVANCEMENT OF ENTERAL FEEDING

The rate of increase of feeding volume in premature infants is variable, as there is no current consensus among physicians. The slowest rate of volume advancement for one neonatal unit may be considered to be the fastest rate for others and vice versa. The decision to start advancing feeding is based on clinical evaluation of tolerance of feedings, which is assessed regularly by checking presence/absence of vomiting and abdominal distention. The routine measurement and evaluation of gastric residuals are of unclear clinical significance. (12)(13) There is no definite evidence to suggest that routine evaluation of gastric residuals in the preterm population provides a good monitoring tool for assessment or prediction of NEC. Although bloody gastric residuals need to be considered seriously, routine low-volume gastric residuals in an otherwise well infant should not affect the advancement of enteral feedings. Several trials have been conducted to study the intestinal motility effects of various medications (eg, erythromycin,


Start feeds at 12ml/kg/day
i.e., 1ml/kg every 2 hours
(Usually happens on day 2 to 3)
After 24 hours
If baby tolerated the above feeds
Double it to 2ml/kg every 2 hours
(24 ml/kg/day of total feeds)
If tolerated for 24 hours
Increase feeds BY 24 ml/kg/day
i.e., by 2ml/kg every 2 hours
(Usually from day 3 to 5)
If continued to be tolerated
Continue increasing feeds by 24ml/kg/day or 2ml/kg every 2 hours until fully enterally fed at 150ml/kg/day
(Every 24 hours)

- If a mother wants to breastfeed, wait at least 48 hours before starting formula feed
- Give colostrum to all babies (mouth care or bolus feed
- If no EBM is available, Hydrolysed Preterm Formula is used to initiate enteral feeds
- If not enough EBM to start regular feeds, give bolus feeds of small EBM produced

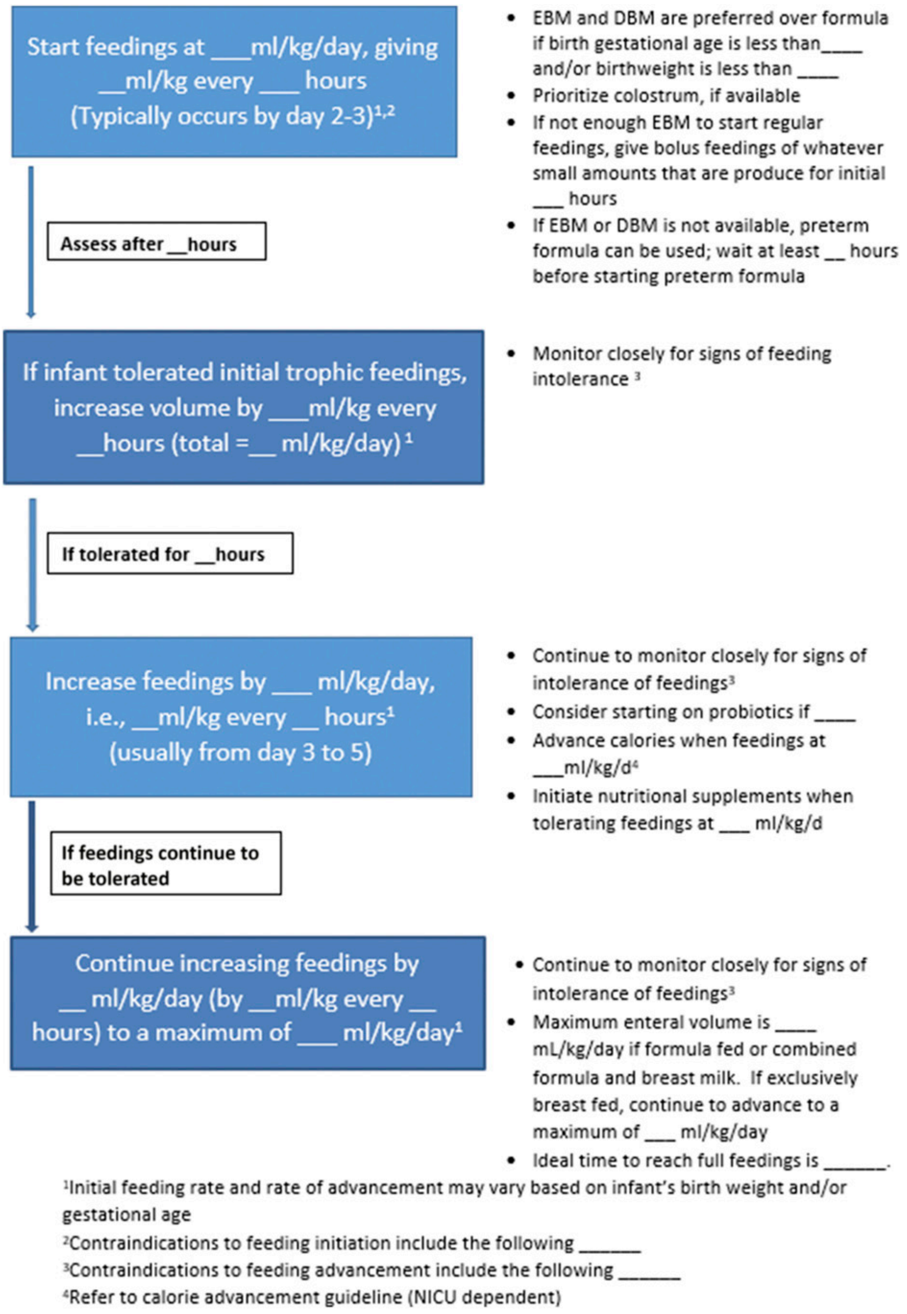
- Close monitoring of any signs of intolerance of feeds
- EBM is preferred milk over any formula feed
- Consider starting on probiotics

- Some babies may tolerate increasing feeds twice a day
- Once fully enterally fed- gradually increase to 165→175ml/kg/day (185ml/kg/day in exclusively breastfed babies) - take step up every 1 to 2 days

Figure 2A. An example of feeding guidelines for infants of less than 32 weeks' gestation and/or less than 1.5 kg birthweight. This reflects current practice in the authors' unit based on multiple factors and has not been previously published or compared with other feeding guidelines in a randomized controlled trial. EBM=expressed breast milk.

lactulose) in achieving full enteral volume. (14)(15) However, use of such medications is not widely accepted. The assessment of tolerance to feedings has subjective variations depending on several factors, including gestational age of the infant, postnatal age, associated clinical and hemodynamic parameters, sepsis-related concerns, the experience of the bedside nurses and physicians, and occasionally, parental anxiety. In addition to the differences in the daily volume or rate of advancement of feedings, variations in advancement may be seen (either once daily or more frequently). There are also differences in whether continuous or bolus feeding is administered, even within the same unit. Of note, no differences have been found between these methods of administration (bolus vs continuous) in the time to achieve full enteral volume, risk of NEC, rapidity of weight gain, or duration of hospitalization. (16)

Many neonatal units around the world have developed their own guidelines for the advancement of enteral nutrition in preterm infants. Some practices are evidence-based, having considered the most current literature, whereas others are "historical" in nature, using the same feeding guidelines that have been in place for years, reflecting a degree of comfort with a particular practice. As mentioned previously, whatever feeding regimen is used, there is evidence that having a standardized practice does have an impact in decreasing NEC frequency. Different concepts of what is considered to be feeding intolerance play an important role in advancing enteral volumes. (17) A particular feeding protocol in one unit may not be suitable or practical in another unit. Fig 2A provides an example of a feeding guideline for premature and low birthweight infants. This regimen is currently in use in our own unit and should only be considered an example of a feeding practice. Clinicians should make their own pragmatic decisions about developing feeding guidelines based on the available evidence, unit preferences, and consensus of the


Start feedings at ___ml/kg/day, giving __ml/kg every ___ hours (Typically occurs by day 2-3)^{1,2}
Assess after __hours
If infant tolerated initial trophic feedings, increase volume by ___ml/kg every __hours (total =__ ml/kg/day)^{1}
If tolerated for __hours
Increase feedings by ___ ml/kg/day, i.e., __ml/kg every __ hours^{1} (usually from day 3 to 5)
If feedings continue to be tolerated
Continue increasing feedings by __ ml/kg/day (by __ml/kg every __ hours) to a maximum of ___ ml/kg/day^{1}

- EBM and DBM are preferred over formula if birth gestational age is less than____ and/or birthweight is less than ____
- Prioritize colostrum, if available
- If not enough EBM to start regular feedings, give bolus feedings of whatever small amounts that are produce for initial ___ hours
- If EBM or DBM is not available, preterm formula can be used; wait at least __ hours before starting preterm formula

- Monitor closely for signs of feeding intolerance^{3}

- Continue to monitor closely for signs of intolerance of feedings^{3}
- Consider starting on probiotics if ____
- Advance calories when feedings at ___ml/kg/d^{4}
- Initiate nutritional supplements when tolerating feedings at ___ ml/kg/d

- Continue to monitor closely for signs of intolerance of feedings^{3}
- Maximum enteral volume is ____ mL/kg/day if formula fed or combined formula and breast milk. If exclusively breast fed, continue to advance to a maximum of ___ ml/kg/day
- Ideal time to reach full feedings is ______.

[1] Initial feeding rate and rate of advancement may vary based on infant's birth weight and/or gestational age

[2] Contraindications to feeding initiation include the following ______

[3] Contraindications to feeding advancement include the following ______

[4] Refer to calorie advancement guideline (NICU dependent)

Figure 2B. A template that neonatal providers can use to develop feeding advancement guidelines in their own units. DBM=donor breast milk; EBM=expressed breast milk.

practitioners regarding multiple factors, such as the use of donor breast milk, maximum enteral feeding volume, timing of adding breast milk fortifiers, and using probiotics, as well as the practice of continuous versus bolus feeding. In Fig 2B we provide a template for readers to consider using when creating feeding guidelines for their own units based on the aforementioned factors.

A single feeding regimen may not be appropriate for the wide range of preterm gestations, for example, 23 to 26 weeks' gestation versus 27 to 31 weeks' gestation. Infants of lower gestation may have considerably different problems and medical needs as compared to more mature preterm infants because of different physiologic and maturational intestinal functions. Hence, our approaches and aspirations to achieve full enteral feedings in these infants need to be realistic. This is also true for infants who may be unwell (eg, hemodynamically unstable) and are in need of significant (or disproportionate) cardiorespiratory support. This was demonstrated in the subgroup analysis of a randomized controlled trial (RCT) conducted in the United Kingdom, which compared early feeding after birth (2 days) with delayed feeding (6 days) in growth-restricted preterm infants with abnormal antenatal Doppler findings (the Abnormal Doppler Enteral Prescription Trial [ADEPT]). (18) The mean gestational age was 31 weeks. The authors found that the early introduction of enteral feedings in growth-restricted preterm infants resulted in earlier achievement of full enteral feeding and did not appear to increase the risk of NEC. The subgroup analysis of this trial showed that full feedings were achieved later in infants of less than 29 weeks' gestation (median age 28 days; interquartile range [IQR] 22-40) compared with 19 days (IQR 17-23) in infants of greater than or equal to 29 weeks' gestation (hazard ratio 0.35; 95% confidence interval [CI] 0.3-0.5). The incidence of all stages of NEC was also higher in this group: 39% (32/83) in infants of less than 29 weeks' gestation compared with 10% (32/312) in those of greater than or equal to 29 weeks' gestation (relative risk [RR] 3.7; 95% CI 2.4-5.7). Hence, the authors concluded that a slower advancement of feedings may be required for this population of infants. (19)

CLINICAL TRIALS COMPARING FEEDING RATES

Over the last 15 years, numerous trials have tried to address the question of optimal rate of feeding advancement in preterm infants. Most of these were RCTs and of good methodological design. During our review of the literature, it was clear to us that the dilemma of slower versus faster rates of feeding volume advancement has long existed. Moreover, the definitions and goals for providing enteral feeding, as well as the rates of advancement, have been changing over the years. One of the earliest comparisons of feeding rates was from the 1970s; the feeding advancement rate that was considered fast at that time is in fact considered a slow rate in recent trials. (20) Almost all recent trials define a slow advancement as a rate of 15 to 20 mL/kg per day and a fast rate as 30 to 40 mL/kg per day. Thus, even with progress in our knowledge of preterm nutrition, some of the long-held beliefs concerning feeding rates and their relationship to NEC may not be evidence-based. Moreover, neonatologists who currently practice may be more at ease with increasing enteral feedings at more liberal rates.

A number of units have enteral volume advancement rates more or less in the middle of slow and faster feeding regimens. We and others may change our practices in the future depending on evidence from well-conducted RCTs. One of the criteria for advancing is the tolerance to the previous volume(s). We acknowledge that the assessment of feeding tolerance can be quite variable and subjective depending on the threshold of individual clinicians. With the exception of the recently conducted Speed of Increasing Milk Feeds (SIFT) trial, virtually all other RCTs assessing rapidity of advancement of enteral volumes have included very small sample sizes. (21)(22) Outcome variables have generally included the number of days to the achievement of full enteral feedings, the number of days to regain birthweight, and the incidence of NEC. There have been some differences in the RCTs based on the type of feedings (expressed breast milk, formula feedings, or a combination). These may have resulted in some of the differences in the results. All published RCTs have been included in a recent systematic review. (21)

RATE OF FEEDING ADVANCEMENT AND SHORT-TERM NUTRITIONAL OUTCOMES

As discussed elsewhere in this article, the reservation about faster rates of feeding advancement is mainly because of the belief that this approach increased the risk of NEC. The evidence supporting this belief is not of high quality (mainly based on observational studies). In fact, a number of published RCTs have concluded the contrary as addressed in the Cochrane review. (21) The population included infants of less than 32 weeks' gestation or birthweight less than 1,500 g. The included trials compared outcomes of infants who were advanced slower (15-20 mL/kg per day) versus those advanced faster (35-40 mL/kg per day). No significant difference was found in the risk of NEC (RR 1.07; 95% CI 0.83-1.39) or in all-cause mortality (RR 1.15; 95% CI 0.93-1.42). In the subgroup analysis, the results were similar in extremely preterm (<28 weeks' gestation) and extremely low birthweight (<1,000 g) neonates. The total number of infants included in the systematic review was 3,753. The RCT contributing the greatest number of infants was the SIFT trial (almost 2,800 infants). The findings from the SIFT trial have not yet been formally published, but investigation data have been presented at various international meetings, (22) as well as in the aforementioned Cochrane review. Jon Dorling, the principal investigator of the SIFT trial has summarized the main outcomes as follows: "At hospital discharge, SIFT did not demonstrate any harms from faster feed increments (30 mL/kg per day vs 18 mL/kg per day), and benefits were seen in terms of reaching full feeds quicker and being given less parenteral nutrition. Indeed, there was more NEC and late-onset sepsis in the slower feed increment group although this did not reach statistical significance. Outcomes at 2 years of age (corrected for prematurity) will be available later this year" (J. Dorling, MBChB, DCH, MD, personal communication, 2018). Details of this study are forthcoming.

CONCLUSION

The weeks after the delivery of an extremely preterm or low birthweight infant are a period of relative nutritional deprivation. Clinicians caring for such infants need to adopt strategies that provide adequate nutrition to this vulnerable population. Optimal strategies should not put infants at increased risk for feeding-related complications. Feeding regimens that are created for this population should be mindful of providing adequate proteins and calories, with the goals of 1) achieving full enteral feeding volume as soon as possible, 2) achieving optimal growth, and 3) perhaps, improving neurodevelopmental outcomes, without increasing the risk for NEC. Admittedly, feeding practices vary widely around the world and not all have a strong evidence base to support them. The debate about slower versus faster advancement of feeding volumes in preterm infants has been subjected to a number of RCTs over the past 2 decades. The results have been reassuring regarding faster rates of advancement without increasing the risk of NEC. With the advancement of our knowledge in neonatal nutrition, clinicians should consider adopting feeding strategies to incorporate new evidence into their clinical practice. Health care providers should also be prepared to challenge and debate the long-held beliefs and practices regarding preterm nutrition. This will help develop rational clinical guidelines that can lead to optimal growth, reduced incidence of NEC, and improved long-term neurodevelopmental outcomes.

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The Rapidity of Advancement of Feedings in Premature Infants: Evidence Basis and Current Recommendations

Shalabh Garg and Sunil Sinha

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Index of Suspicion in the Nursery

1 Multiple Fractures at Birth

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AUTHOR DISCLOSURE Drs Gans, Underland, Levin, and LaTuga have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female neonate is born at 33 weeks of gestation via urgent cesarean section secondary to severe preeclampsia with hemolysis, elevated liver enzymes, and low platelet count syndrome. On examination, her weight is 1.18 kg (1st percentile), length 39.5 cm (5th percentile), and head circumference 27 cm (1st percentile). She is well appearing with white sclera, normal tone, and appropriate reflexes. She has scaphocephaly, a soft skull, proptosis with shallow orbits, low-set ears, swelling of the right wrist, a widened fontanelle, prominent knobs along her ribs, and frontal bossing. Laboratory results are notable for normal serum calcium, low serum phosphorous, elevated parathyroid hormone, low 25-hydroxyvitamin D, elevated 1,25-dihydroxyvitamin D, normal urine electrolytes, and negative findings on New York State newborn screening (Table 1). Radiographs obtained shortly after birth show bony demineralization, metaphyseal flaring particularly at the wrists and knees, metaphyseal fractures, and bilateral rib fractures (Fig). The maternal history is significant for 5 previous miscarriages, nonadherence with taking prenatal vitamins, a diet containing minimal dairy products, and modest dress for religious observance, with limited skin exposure to natural sunlight. The parents are consanguineous.

DISCUSSION

The neonate is diagnosed with congenital rickets with secondary hyperparathyroidism complicated by in utero fractures, likely secondary to maternal vitamin D deficiency. Congenital rickets secondary to vitamin D deficiency is extremely rare with only 25 cases published to date. (1)

In humans, vitamin D3 is synthesized after exposure to sunlight, metabolized in the liver to its storage form, 25-hydroxyvitamin D, and converted in the kidney by 1-α-hydroxylase to its active form, 1,25-dihydroxyvitamin D. 1,25-Dihydroxyvitamin D is primarily responsible for absorption of vitamin D and phosphorous in the gastrointestinal tract. Parathyroid hormone (PTH) increases serum calcium through bone reabsorption in addition to stimulating renal phosphorous excretion. In the setting of vitamin D deficiency, calcium cannot be absorbed through the gastrointestinal tract; maintenance of serum calcium is driven by PTH, which enhances calcium absorption from bone. (2) Veiled women who lack ultraviolet light exposure are at particularly high risk for vitamin D deficiency. (3) During pregnancy, vitamin D deficiency may be prevented by maternal sun exposure, dietary vitamin D intake, and prenatal vitamins. (4)

Congenital rickets secondary to maternal vitamin D deficiency from limited sun exposure and/or diminished oral intake causes bone disease in utero, which

TABLE 1. **Initial Laboratory Testing**

LABORATORY TEST	RESULT	REFERENCE
Phosphorous, mg/dL (mmol/L)	3.8 (1.2)	4-6.5 (1.3-2.1)
Calcium, mg/dL (mmol/L)	8.3 (2.08)	6.2-11 (1.5-2.7)
Parathyroid hormone, pg/mL (ng/L)	909.5 (909.5)	1-43 (1-43)
Alkaline phosphatase, U/L (μkat/L)	1,038 (17.3)	63-483 (1.05-8.07)
25-hydroxyvitamin D, ng/mL (nmol/L)	14.3 (36)	>30 (>75)
1,25-dihydroxyvitamin D, pg/mL (pmol/L)	388 (1,009)	31-87 (81-226)
Urine phosphorous, mg/dL (mmol/L)	8 (2.6)	7-148 (2.2-47.8)
Urine calcium, mg/dL (mmol/L)	4.2 (1.05)	0.5-35.7 (0.13-9)
Urine creatinine, mg/dL (μmol/L)	15.2 (1,344)	15-327 (1,326-28,907)
New York State Newborn Screening	Negative	Negative

can lead to fractures. These patients have low 25-hydroxyvitamin D with hyperparathyroidism, elevated alkaline phosphate, and decreased phosphorous. Characteristic findings of metaphyseal cupping on bone radiography may aid in diagnosis. (2) However, information on the minimum amount of vitamin D required for proper growth in the developing fetus and neonate is limited. Despite the lack of normative data for neonatal vitamin D requirements, this neonate's 25-dihydroxyvitamin D level was not as low as would have been expected in the setting of congenital rickets. We hypothesize that the patient's mother may have had increased vitamin D exposure toward the end of her pregnancy. The patient's clinical history and laboratory findings are not consistent with other causes of rickets. Data regarding the long-term effects of in utero vitamin D deficiency on the development of the brain and other organs are limited.

Other causes of rickets include abnormal vitamin D metabolism from known genetic mutations, multiorgan failure, and inadequate intake or sun exposure, each with characteristic laboratory (Table 2) and clinical findings. In terms of mutations, pseudovitamin D deficiency rickets results from a mutation in 1-α-hydroxylase with subsequent low 1,25-dihydroxyvitamin D levels. These infants respond to 1,25-hydroxyvitamin D replacement. In hereditary vitamin D-resistant rickets, a mutation in the vitamin D receptor causes affected infants to have a limited

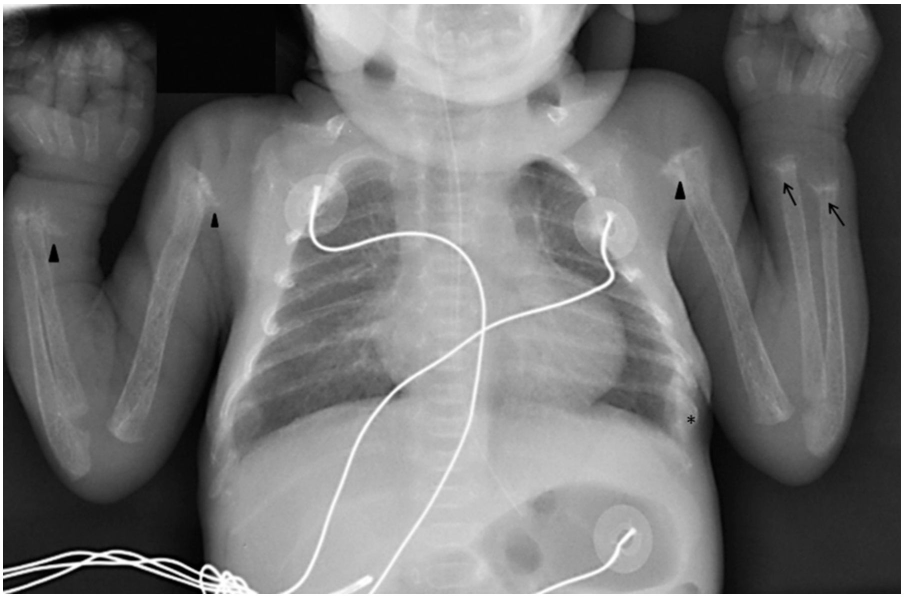

Figure. Frontal view of the chest demonstrates bone demineralization, flaring of the metaphyses at the wrist (arrows), and metaphyseal fractures (arrowheads). Bilateral rib fractures are noted (asterisk). Knee films demonstrated similar metaphyseal findings in the distal femora and proximal tibiae.

TABLE 2. **Differential Diagnosis of Rickets in Infancy**[a]

DIAGNOSIS	SERUM CALCIUM	SERUM PHOSPHORUS	PARATHYROID HORMONE	25-HYDROXYVITAMIN D	1,25-DIHYDROXYVITAMIN D	ALKALINE PHOSHATASE	URINE CALCIUM	URINE PHOSPHOROUS
Vitamin D deficient rickets	↓ NL	↓	↑	↓	↑NL	↑	↓	↑
Pseudovitamin D deficiency rickets	↓ NL	↓	↑	NL	↓	↑NL	↓	↑
Hereditary vitamin D-resistant rickets	↓ NL	↓	↑	NL	↑↑	↑	↓	↑
Familial hypophosphatemic rickets	NL	↓↓	↓NL	NL	↓	↑	↓	↑
Hereditary hypophosphatemic rickets with hypercalciuria	NL	↓↓	↓NL	↓NL	↑	↑	↑	↑
Renal osteodystrophy	↓NL	↑	↑	NL	↓	↑	↓NL	↓
Rickets of prematurity	NL	↓	↑NL	NL	↑	↑	NL	NL
Oncogenic rickets	NL	↓	NL	NL	↑	↑	↓	↑

[a] *Laboratory findings compared with standardized values are normal limits (NL), elevated (↑), or decreased (↓).*

response to high-dose calcium and vitamin D supplementation. Infants with familial hypophosphatemic rickets typically inherit an X-linked mutation affecting the PHEX protein, which inhibits renal phosphate absorption. These infants have decreased phosphate and 1,25-dihydroxyvitamin D without hyperparathyroidism, and 1,25-hydroxyvitamin D levels are replaced as treatment. In hereditary hypophosphatemic rickets with hypercalciuria, renal phosphate wasting causes an increase in 1,25-dihydroxyvitamin D levels and urine calcium excretion without hyperparathyroidism. These infants are treated exclusively with phosphate replacement.

Rickets may present as a component of renal osteodystrophy, which occurs in patients with chronic kidney disease when the damaged kidneys cannot convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and cannot excrete phosphate. This leads to secondary hyperparathyroidism and is managed with vitamin D replacement, phosphate binders, restriction of dietary phosphate, and dialysis. (2) Rickets of prematurity is most common among infants born weighing less than 1,500 g who have inadequate calcium and phosphate intake and requires replacement of minerals. (5) Lastly, paraneoplastic tumors can excrete substances that reduce renal phosphate absorption, leading to oncogenic rickets. Optimal treatment is tumor resection, but patients may also receive supplementation with phosphate and 1,25-dihydroxyvitamin D. (2)

MANAGEMENT

The neonate described herein was given calcium (25 mg/kg per day) and high-dose vitamin D (6,000 U) supplementation. Within a few weeks of supplementation, laboratory findings corrected and physical examination findings improved. The neonate's response to therapy supports the diagnosis of congenital rickets resulting from maternal vitamin D deficiency. The neonate was then transitioned to standard-dose vitamin D (400 U), calcium (12.5 mg/kg per day), and iron (4 mg/kg per day). The infant was fed 22 kcal/oz formula and discharged from the hospital at 39 weeks' corrected gestational age. The mother was given vitamin D supplementation and counseled regarding future pregnancies. The infant currently has gross motor delay at 12 months of age.

Lessons for the Clinician

- Etiology of rickets requires careful consideration of calcium, phosphorous, parathyroid hormone, and vitamin D values; clinical history; and response to therapy.
- Evaluation of a neonate with multiple fractures at birth should include a thorough maternal dietary history once other causes of fractures, such as nonaccidental trauma, have been excluded.

- Neonates born to mothers with modest dress for religious reasons with limited vitamin D supplementation during pregnancy are at risk for vitamin D-deficient rickets.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the interrelated effects of various hormones, including parathormone, calcitonin, and vitamin D on calcium, phosphorus, and magnesium metabolism in the fetus and neonate.

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Case 1: Multiple Fractures at Birth

Melissa D. Gans, Lisa Underland, Terry L. Levin and M. Susan LaTuga

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2 Newborn with Acute-Onset Central Cyanosis

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AUTHOR DISCLOSURE Drs Gosavi, Murki, and Kiran have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant of 31 weeks' gestational age and birthweight of 1.19 kg is born to a gravida 2 woman. The mother had received a complete course of antenatal steroids 2 days before delivery. There is no history of early infantile deaths, early-onset stroke, or coronary heart disease in any of the family members.

The infant is delivered via cesarean section for fetal bradycardia and maternal eclampsia. At birth, she requires resuscitation with bag and mask for 1 minute, which is followed by delivery room continuous positive airway pressure (CPAP). Respiratory distress in the immediate neonatal period is supported with bubble CPAP in the first 48 hours after birth. For hemodynamically significant patent ductus arteriosus (PDA), the newborn is treated with diuretics, inotropes, and then ibuprofen syrup from day 3 to day 6 after birth. Echocardiography performed on day 6 after birth shows a closed PDA and no structural heart defect or vegetation. On day 8 after birth, in view of recurrent apneas, positive sepsis screen, and a positive blood culture for coagulase-negative *Staphylococcus*, the infant is given intravenous vancomycin. Her general condition is improving; she is tolerating feeds and is being transferred to a stepdown unit.

On day 14 after birth, the infant develops repeated desaturations, which progress to recurrent apnea over the duration of 12 hours. She continues to require an increasing fraction of inspired oxygen (FiO_2), bubble CPAP, and then ventilation with 100% FiO_2. On examination, the infant has central cyanosis, lethargy with decreased spontaneous activity, normal capillary refill time, and well-palpable pulses. Noninvasive blood pressure is 62/37 mm Hg with a mean arterial pressure of 45 mm Hg. The infant's urine output is 1.5 mL/kg per day and there is no evidence of abnormal weight gain, murmur, or abnormal heart sounds. The heart rate is consistently in the normal range. Even when receiving mechanical ventilation with 100% $FiO_{2,}$ the newborn has central cyanosis with saturation in the range of 78% to 80%. Oxygen saturations in all 4 limbs are similar. The respiratory system is normal, with normal breath sounds and equal air entry on both sides. The infant shows no evidence of abnormal body movements or seizure activity.

The infant has a blood glucose measurement of 85 mg/dL (4.7 mmol/L); serum electrolyte measurements show a sodium level of 135 mEq/L (135 mmol/L), potassium of 3.9 mEq/L (3.9 mmol/L), and chloride of 103 mEq/L (103 mmol/L). On complete blood cell count evaluation, the infant has a hemoglobin level of 15 g/dL (150 g/L), packed red blood cell volume of 44.5%, total white blood cell count of 24,000/μL (24×10^9/L) with 60% neutrophils, and platelet count of 65×10^3/μL (65×10^9/L). Coagulation profile shows a prothrombin time of 14.1 seconds, activated partial thromboplastin time of 44.8 seconds, fibrinogen level of

289 mg/dL (3.89 g/L), and C-reactive protein of 4.2 mg/L (40 nmol/L). Arterial blood gas shows a pH of 7.31, PaO_2 of 44 mm Hg (5.8 kPa), PCO_2 of 38.5 mm Hg (5.1 kPa), and base excess of −6.5. There is no evidence of methemoglobinemia; neurosonography findings are normal. Another investigation conducted at this point reveals the diagnosis.

DISCUSSION

Echocardiography showed large right atrial thrombus obstructing tricuspid flow intermittently with right to left flow through a patent foramen ovale (PFO) (Fig 1). Severe desaturations with normal pulse and normal blood pressures suggested a right to left flow through the PFO. Absence of difference in saturations between right upper and lower limb also suggested a shunt across the PFO. Negative sepsis screen with normal chest radiograph ruled out pneumonia. Low PaO_2 with low oxygen saturation and normal methemoglobin levels ruled out methemoglobinemia. There was no evidence of pulmonary hemorrhage clinically or on chest radiography.

The presence of umbilical line and coagulase-negative staphylococci sepsis may have contributed to the genesis of right atrial thrombus in this newborn. Absence of thrombus with a normal echocardiogram on day 6 after birth when documenting PDA closure suggested that the onset of thrombus was after that day. Progressive increase in size with consumption of platelets resulted in repeated desaturation, apneas, and thrombocytopenia. Lethargy and hypotonia were due to hypoxia.

MANAGEMENT

The newborn was treated with mechanical ventilation, fluid bolus, and inotropic support. A percutaneous intravenous central line was introduced in the right upper limb, ensuring that the tip was placed in the right atrium. The tip position was confirmed with chest radiography. Thrombolysis was attempted with recombinant tissue plasminogen activator at 0.1 mg/kg per hour for 6 hours. The infant also received platelet and fresh frozen plasma transfusion during this time. After 6 hours of thrombolysis, echocardiography showed significant reduction in the size of the atrial thrombus and a clinical improvement in saturations. Unfractionated heparin was started at 15 U/kg per hour, continued for the next 24 hours, and switched to subcutaneous low-molecular-weight heparin. Repeated echocardiography showed dramatic reduction in the size of the thrombus (Fig 2). The infant underwent extubation after 48 hours and was breathing room air by the next 48 hours. Intravenous vancomycin was continued for 10 days. Repeat blood culture for bacteria and fungi were sterile, and urine culture for fungus was also negative. The neonate received maintenance low-molecular-weight heparin until resolution of atrial thrombus and for 2 weeks.

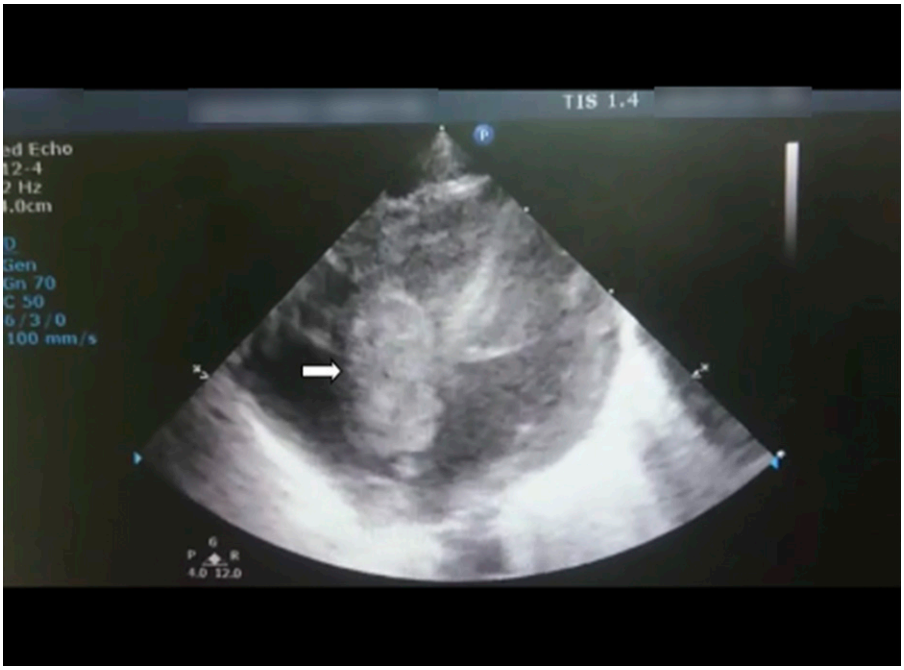

Figure 1. Large right atrial thrombus obstructing the tricuspid valve (arrow).

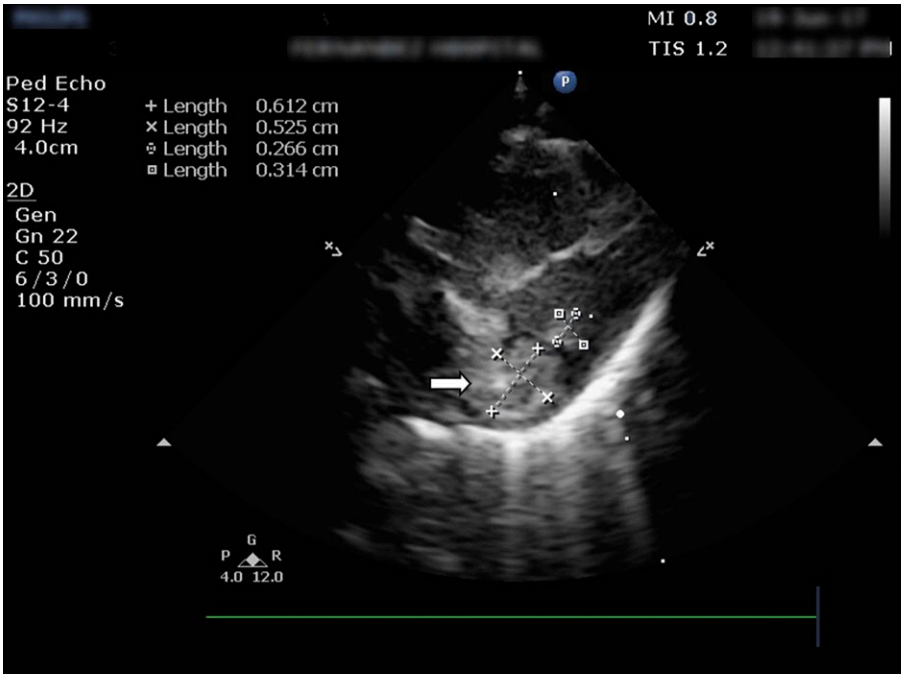

Figure 2. Atrial thrombus after 5 days of treatment (arrow).

NEONATAL THROMBOEMBOLISM

The incidence of neonatal thromboembolism is 6.8 per 1,000 NICU admissions. (1) The incidence remains the same in term versus preterm neonates as well as in male versus female neonates. (1) The neonatal coagulation system differs from those of children and adults, with a higher level of factor VIII and von Willebrand factor activity and low levels of factors II, VII, IX, X, XI, and XII. (2) These differences place the neonate in a relative prothrombotic state. Umbilical venous catheters and peripheral central venous catheters are commonly used in neonates. One study found that 21.4% of 28 infants with umbilical venous catheters had thrombus formation. (3) In neonates, intracardiac thrombosis is a rare event, with the incidence reported to be between 0.7 and 2.4 per 1,000 admissions; almost 90% of these are related to the use of central venous catheters. Intravascular catheters act as a nidus for platelet and fibrin accumulation and can damage the endothelium. (4)(5) Intracardiac (mainly right atrial thrombi) thrombosis is life-threatening because of the risk for dissemination of emboli into the lungs, obstruction of the right pulmonary artery, and obstruction of the tricuspid valve producing a pure right to left shunt across the PFO. (6)(7)

Lessons for the Clinician

- Intracardiac thrombosis is a life-threatening complication.
- Acute/subacute onset severe cyanosis, no lung findings, and absence of differential cyanosis should point to a right to left shunt across a patent foramen ovale.
- Thrombolytic therapy, mainly recombinant tissue plasminogen activator, for use in neonates, should be reserved for limb, organ, and/or life-threatening thromboses, including right atrial thromboses.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the causes and clinical manifestations of catheter complications of parenteral nutrition.
- Know the causes and pathophysiology of neonatal thrombocytopenia and thrombocytosis.
- Know the clinical and laboratory manifestations and management of neonatal thrombocytopenia and thrombocytosis.

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Case 2: Newborn with Acute-Onset Central Cyanosis

Rahul S. Gosavi, Srinivas Murki and Sai Kiran

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3 Premature Infant with Anemia and High-Output Cardiac Failure

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AUTHOR DISCLOSURE Drs Weiner, Talmon, Peniakov, and Felszer-Fisch have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female singleton is delivered at 30 6/7 weeks' gestational age via cesarean for preterm labor and breech presentation. The mother is a 37-year-old grand multipara in her 10th pregnancy. The pregnancy is notable for severe fetal anemia, high-output cardiac failure with normal cardiac anatomy, polyhydramnios, and a placental chorioangioma diagnosed at 26 weeks of gestation. Evaluation for congenital infections is negative. At 25 and 28 weeks' gestation, the fetus had received in utero red blood cell transfusions for severe fetal anemia.

At birth, the infant has respiratory depression requiring intubation and ventilation. Apgar scores are 7, 6, and 8 at 1, 5, and 10 minutes, respectively, and her birthweight is 1,416 g. The neonate is noted to have a protuberant abdomen with significant hepatosplenomegaly, diffuse subcutaneous edema, petechiae, and ecchymoses.

The infant requires significant ventilator support for the first few weeks after birth. Chest radiography shows no evidence of pleural or pericardial effusion. Echocardiography shows normal cardiac segmental anatomy with significant biventricular hypertrophy, though blood pressure is maintained. Significant anemia, thrombocytopenia, and coagulopathy are noted over the first days after birth, for which the newborn requires multiple blood products. Profound jaundice necessitates multiple double-volume exchange transfusions. Thrombocytopenia and coagulopathy gradually improve over the first week after birth. However, the infant develops significant cholestasis, reaching a peak direct bilirubin of 12.5 mg/dL (213.8 μmol/L) at 2 weeks of age.

DISCUSSION

The unique constellation of findings in this case, anemia, thrombocytopenia, high-output failure, and cholestasis, presented a broad differential diagnosis. The differential included congenital heart disease and vascular malformations, infectious etiologies, metabolic and genetic disorders, and various renal, hepatic, gastrointestinal, and hematologic pathologies. Sepsis evaluation was performed on admission and cultures were sterile. Evaluation for congenital infections and metabolic/genetic disorders was unremarkable. The infant was diagnosed with glucose-6-phosphate dehydrogenase (G6PD) deficiency, which may have contributed to the jaundice, but was not the sole reason for the profound cholestasis.

Abdominal ultrasonography revealed hepatosplenomegaly with 3 vascular lesions in the liver. Abdominal computed tomography scan further supported the diagnosis of hepatic hemangiomas (Fig 1A), with tapering of the abdominal aorta below the celiac trunk suggesting the presence of hepatic arteriovenous shunting (Fig 1B). The infant received treatment with phenobarbital and ursodiol for the cholestasis, without significant improvement. Significant ventricular hypertrophy with left ventricular outflow tract (LVOT) obstruction and restrictive cardiac physiology resulted in elevated left atrial pressure and pulmonary congestion. In an attempt to reduce the size of the liver hemangiomas and improve the hypertrophic cardiomyopathy, treatment with propranolol was started on day 6 and the dose was gradually increased as tolerated.

The infant's clinical condition subsequently improved and she was weaned from ventilator support. The hepatic hemangiomas decreased in size and the cholestasis resolved. Phenobarbital and ursodiol therapy were discontinued. Several weeks later, although the LVOT resolved, the biventricular hypertrophy improved only minimally. At 2 months of age, a cutaneous hemangioma was noted on the abdomen. No further cutaneous hemangiomas were identified over the remaining hospital course.

The infant was discharged from the hospital at 3 months of age with mild chronic lung disease and mild residual hypertrophic cardiomyopathy on low-flow nasal oxygen and propranolol. At 12 months of age, she was receiving propranolol but was weaned from oxygen. She had mild developmental delay and slow growth but was otherwise healthy. Liver ultrasonography showed complete resolution of the hepatic hemangiomas.

Diagnosis

The diagnosis was infantile hepatic hemangioma (IHH).

Pathophysiology

The clinical presentation, imaging findings, later appearance of a cutaneous hemangioma, and clinical improvement in response to propranolol therapy are all highly characteristic of IHH.

Infantile hemangioma is the most common vascular tumor seen in early infancy. It is a benign proliferation of endothelial cells that undergo a phase of rapid growth followed by spontaneous involution. The reported incidence is approximately 5% of healthy infants, and these lesions are more common in premature infants. (1) The term *benign neonatal hemangiomatosis* has been used to describe infants with numerous cutaneous hemangiomas without extracutaneous involvement, whereas diffuse or disseminated neonatal hemangiomatosis describes infants with both cutaneous and visceral hemangiomas.

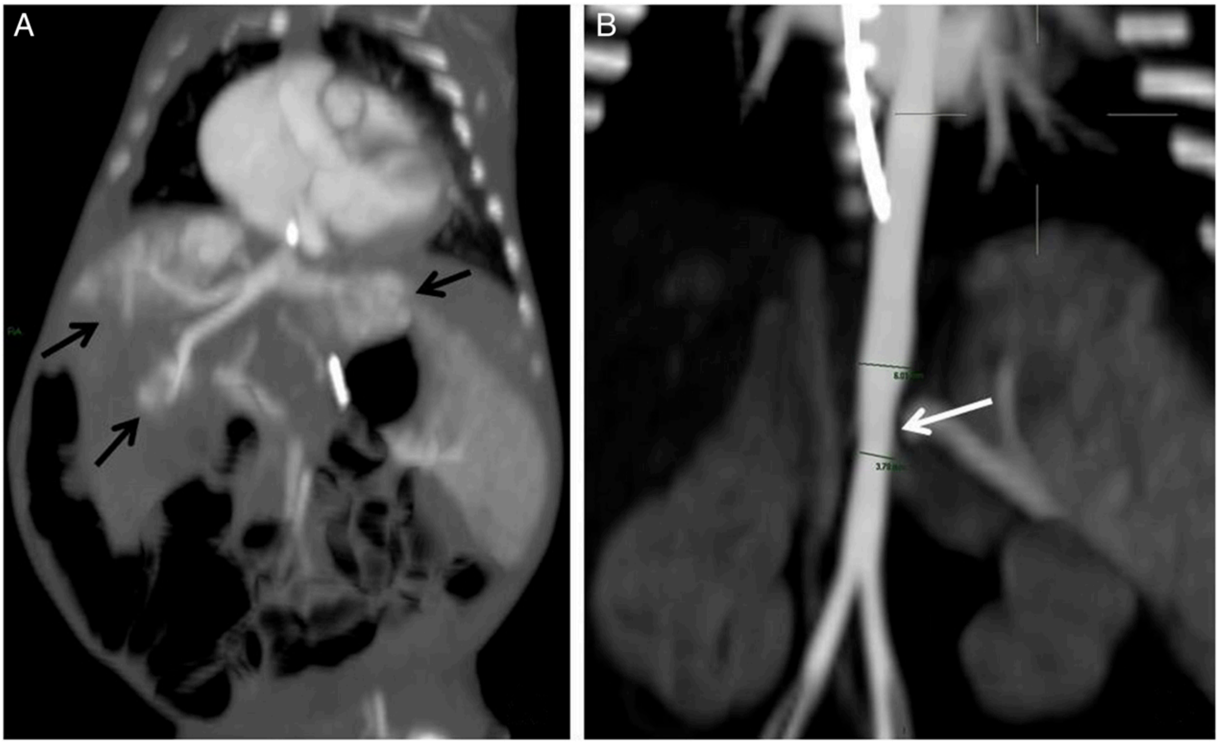

Figure 1. Computed tomography scan. A. Black arrows indicate locations of hepatic hemagiomas. B. White arrow demonstrates aortic tapering below celiac trunk.

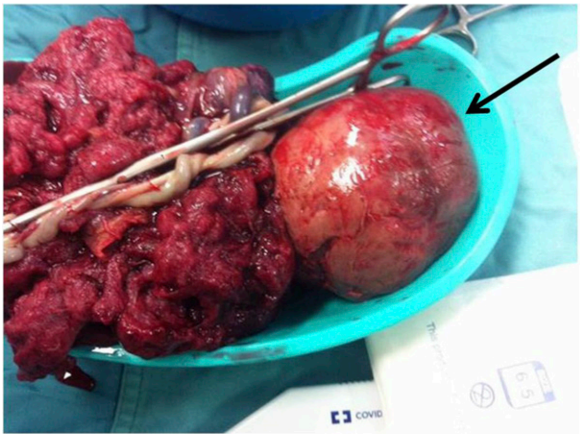

Figure 2. Placenta with chorioangioma. Black arrow indicates the chorioangioma, a firm, well-circumscribed mass measuring 10 cm in its greatest dimension, attached to the placenta.

(2) The latter has a significant mortality rate. The liver is the most common site for a visceral hemangioma, but the gastrointestinal tract, airway and lungs, central nervous system, and eyes may also be affected. Complications include high-output cardiac failure, visceral hemorrhage, and hypothyroidism.

Christison-Lagay et al proposed a subtype classification for IHH: focal, multifocal, and diffuse. (3) A review of this subtype classification approach suggested that focal lesions may represent a process biologically distinct from multifocal and diffuse disease, and most undergo spontaneous involution after birth. (4) This patient's lesion best meets the criteria of a multifocal hepatic hemangioma because the hepatic lesions continued to proliferate after birth and because of the presence of multiple hepatic lesions.

The initial course of the patient was complicated by severe hemolysis and profound cholestasis. It is likely that the rare combination of 3 pathologic hemolytic processes created the need for multiple exchange transfusions: a large placental chorioangioma, a multifocal hepatic hemangioma, and partial G6PD deficiency.

A unique aspect of the case was the finding of a placental chorioangioma measuring 8×8×10 cm (Fig 2). Placental chorioangioma is the most common benign tumor of the placenta, occurring in 1% of all examined placentas. Large tumors, those greater than 4 to 5 cm, are rare and associated with maternal and fetal complications, including polyhydramnios, fetal high-output cardiac failure and cardiomegaly, fetal hydrops, fetal anemia, and neonatal hemolytic anemia. Interestingly, multiple reports of neonatal hemangiomatosis occurring in association with large placental chorioangiomas can be found throughout the medical literature. (5) Both placental chorioangioma and infantile hemangioma are benign proliferations of capillary endothelial cells, suggesting perhaps a common genetic mechanism or a shared trigger leading to a disturbance in embryonic mesodermal development in these patients. The "placental hypothesis" suggests that the pathogenic hemangioma precursor cell may derive from placental progenitor cells. (6)

The cardiac complications seen in this patient were likely the result of high-output cardiac failure related to the large placental chorioangioma, further compounded by the hepatic hemangioma. Despite the removal of the placental chorioangioma from the systemic circulation at birth, the cardiomyopathy, hemolysis, and liver dysfunction progressively worsened over the first weeks after birth, suggesting that the ongoing disease was secondary to the hepatic hemangioma. It could be argued that the rapid clinical improvement may have been the result of absence of the hemodynamic effects of the chorioangioma and/or the cessation of exposure to growth factors or mediators of angiogenesis possibly elaborated by the chorioangioma. Alternatively, it is possible that the hepatic lesion was "preprogrammed" to rapidly involute, as is typical, to a focal hepatic hemangioma. However, the timing of the clinical improvement, coinciding with the increased propranolol dosage and the subsequent shrinkage of the hepatic hemangiomas, argues that propranolol was the main driver of clinical improvement.

Management

Historically, systemic corticosteroid therapy has been the first-line agent for the treatment of IHH, with only limited success. Other agents (eg, interferon) have been no more effective and carry considerable risk of various concerning side effects. In addition, arterial embolization/ligation and surgical resection have been used as alternative treatment strategies. Over the past decade, propranolol has emerged as an effective treatment for severe infantile hemangiomas. (7) In the wake of this discovery, a growing body of clinical reports has described clinical response of IHH to propranolol. (8)(9) This patient similarly responded to propranolol without any side effects.

Lessons for the Clinician

- Infantile hepatic hemangioma may lead to high-output cardiac failure and may cause significant morbidity and mortality.
- Propranolol should be considered as a therapeutic option for infantile hepatic hemangioma.
- Large placental chorioangiomas have been found in association with hepatic hemangiomas and should prompt screening liver ultrasonography in the neonatal period.

ACKNOWLEDGMENTS

The authors wish to thank Drs Christison-Lagay, Etty Daniel-Spiegel, Amichai Rothstein, and Eric Shinwell for their assistance in preparing this article.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical and laboratory features and management of hemangiomas in the newborn.

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Case 3: Premature Infant with Anemia and High-Output Cardiac Failure

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Old Problem, New Solution

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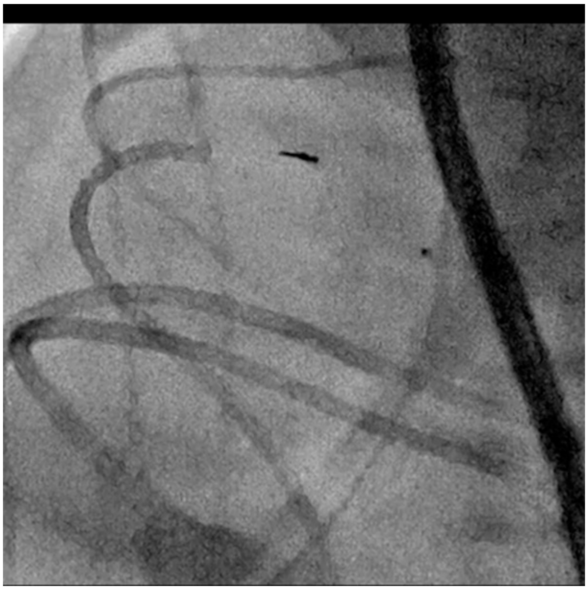


Video 1. Click here to view the video.

QUESTION

What procedure is being performed in Video 1? Select one of the following responses:

A. Atrial septal defect closure
B. Ventricular septal defect closure
C. Patent ductus arteriosus closure
D. Pulmonary valvotomy
E. No therapeutic intervention, only a diagnostic catheterization

CRITIQUE

Patent ductus arteriosus (PDA) is a common complication of prematurity. Video 1 is from the cardiac catheterization of a 3-week-old female infant born at 28 weeks' gestation with a birthweight of 960 g (27th percentile), length of 36 cm (39th percentile), and head circumference of 25.5 cm (42nd percentile). The infant had a hemodynamically significant PDA that did not respond to acetaminophen therapy. Echocardiography showed a moderate to large PDA with left heart dilation, and hence, at 23 days of age (weight 1,160 g), she met the indications for intervention.

AUTHOR DISCLOSURE Dr Rockefeller has disclosed that he is a site principal investigator for an industry-sponsored patent ductus arteriosus closure device trial. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

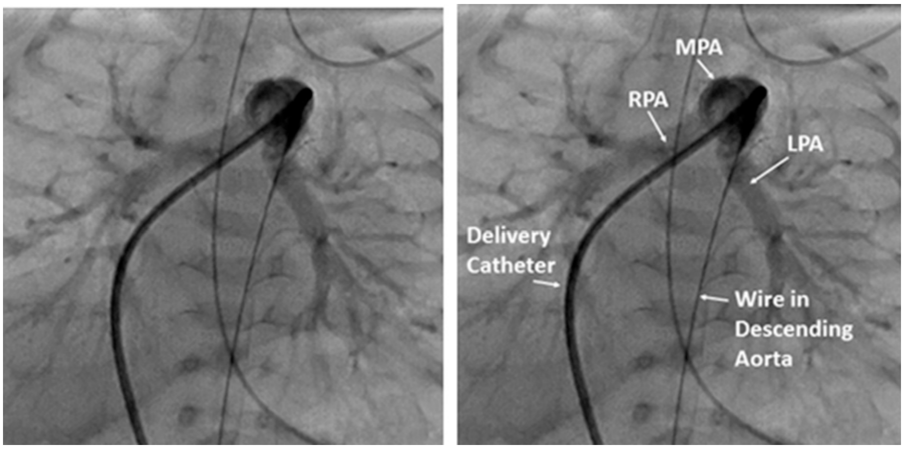
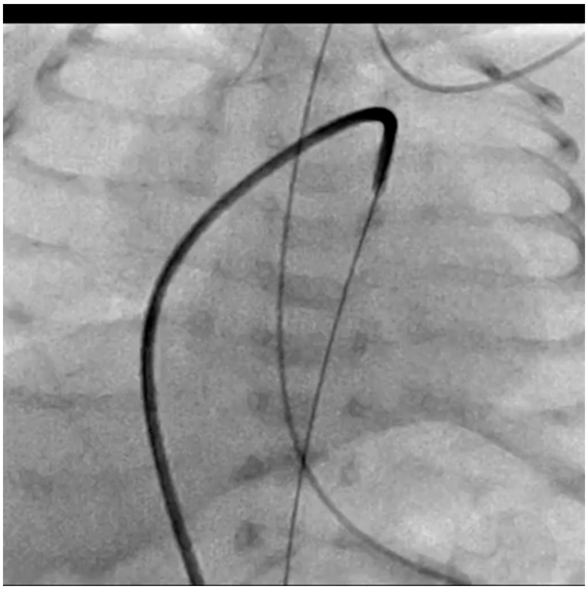


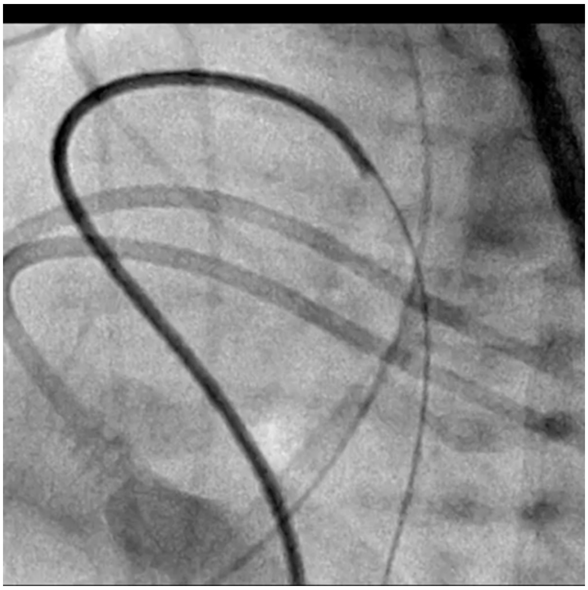
Figure 1. Angiogram (unlabeled and labeled) showing normal-sized branch pulmonary arteries. This image is a clip from Video 2. LPA=left pulmonary artery; MPA=main pulmonary artery; RPA=right pulmonary artery.

Hemodynamically significant PDAs that are unresponsive to medical treatment have, until recently, required surgical ligation via lateral thoracotomy. The associated morbidity for surgical ligation includes pneumothorax, bleeding, recurrent laryngeal nerve injury, and postoperative pain. (1) In an effort to minimize morbidity, Zahn et al reported a case series in 2015 of 6 extremely preterm infants undergoing catheter-based closure of the PDA at a median weight of 1,180 g. (2) Their novel technique minimized contrast dose and radiation exposure by using intraprocedural echocardiography as the primary imaging modality. Since their initial report in 2015, multiple centers across the United States have embraced catheter-based therapies and several have reported on their efficacy. (3) Device closure has been reported to reduce the respiratory severity score, defined as a product of mean airway pressure (MAP) and fraction of inspired oxygen (Fio_2)—MAP × Fio_2. (4) Device closure is now thought to be associated with less morbidity when compared with surgical ligation, but comparison studies are lacking.

In the United States, 2 devices are used for PDA occlusion in preterm infants. One is a multilobed plug made of woven nickel-titanium wire, and the other is a wire frame covered with a polytetrafluoroethylene membrane. Both have multiple size options, low-profile delivery systems, and controlled release mechanisms that allow for precise positioning. Before placing the device, angiography is performed to measure the ductus arteriosus. Based on these measurements, an appropriate occlusion device is selected and the appropriate delivery catheter is advanced over the guidewire into the descending aorta. Video 2 shows an angiogram obtained before device closure of the PDA. In this procedure, a 4-French coronary catheter was advanced antegrade over a guidewire. The guidewire was then positioned in the descending aorta by crossing the PDA antegrade. In this video, the ductus and descending aorta can be seen only briefly, but the branch pulmonary arteries are delineated well. The branch pulmonary arteries are of normal size. The structures are depicted in Fig 1.



Video 2. Click here to view the video.



Video 3. Click here to view the video.

Video 3 shows the same ductal angiogram, but from a straight lateral projection. The course of the guidewire is from the inferior vena cava, through the right atrium, right ventricle, main pulmonary artery, across the PDA, and down the descending aorta. In this video, the PDA and descending aorta are briefly opacified and a dilated main pulmonary artery and normal-sized branch pulmonary arteries are visible (Fig 2).

Video 1 shows a 7.5 frame/second fluoroscopy procedure performed during device release. The device has both proximal and distal radiopaque markers. It is initially connected to the delivery cable, which has been advanced out of the 4-French delivery catheter. The device is positioned within the PDA, and the delivery cable is carefully unscrewed. After detaching from the device, the delivery cable is withdrawn into the delivery catheter. The device remains in good position after release (Fig 3). The device can be visualized on chest radiography (Fig 4) and can be misinterpreted as a foreign body unless the radiologist is aware of the history of the procedure. The 2 different closure devices have distinct radiographic appearances.

After device closure of a PDA, a pressure dressing is applied over the groin to prevent bleeding. Although arterial access is not routinely obtained for PDA closure, the neonate's distal lower extremity pulses should be palpated immediately after the procedure and at regular intervals until the pressure dressing is removed. Arterial spasm and/or thrombosis do not usually occur unless the artery was injured during attempted venous access. After the procedure, a ductal murmur is no longer appreciated. However, a soft systolic murmur due to trivial flow disturbances around the device is occasionally auscultated after the procedure. Echocardiography is typically performed the day after the procedure to confirm stable device positioning and assess for any residual shunting across the PDA. Additional routine follow-up consists of a physical examination and transthoracic echocardiography usually at 1 month, 6 months, and 12 months after the procedure. If there is residual shunting, then the patient is followed every 1 to 3 years thereafter. Otherwise, the patient could be discharged from follow-up. Subacute bacterial endocarditis prophylaxis is indicated in patients with residual shunting due to incomplete endothelialization of the prosthetic material.

Backes et al recently described PDA device occlusion in 747 low-weight infants (<6 kg) and found that 94.4% of

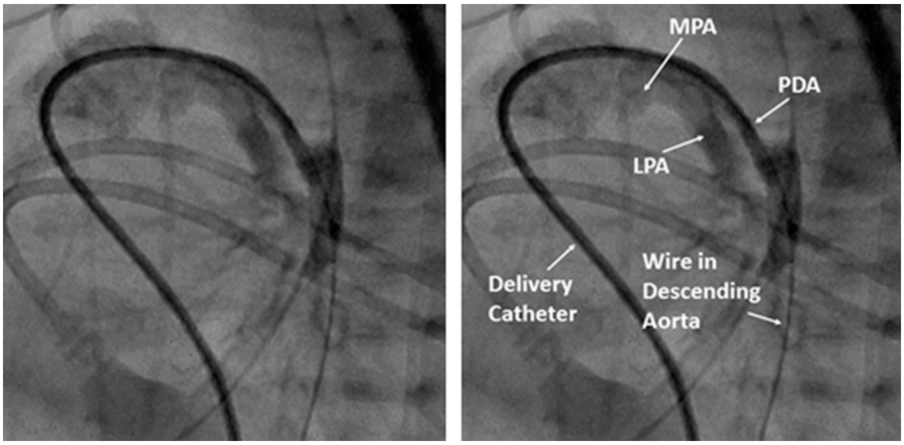


Figure 2. Angiogram (labeled and unlabeled) showing a straight lateral projection. This image is a clip from Video 3. LPA=left pulmonary artery; MPA=main pulmonary artery; PDA=patent ductus arteriosus; RPA=right pulmonary artery.

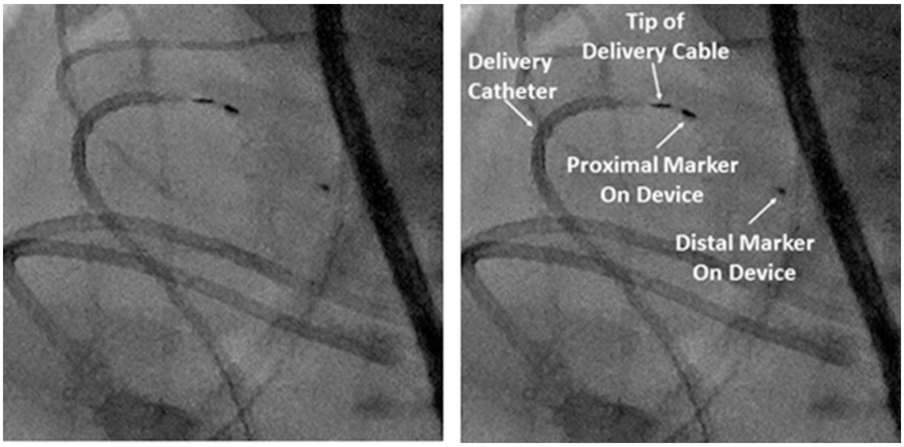


Figure 3. Fluoroscopy (unlabeled, labeled) depicting placement of the device within the patent ductus arteriosus immediately after detaching from delivery cable. This image is a clip from Video 1.

cases achieved technical success. (5) Of the 5.6% deemed to be unsuccessful, 3.2% had device malposition (ie, partial occlusion of left pulmonary artery or aorta) and 2.4% had device embolization. Importantly, the authors found no difference in success rate based on patient weight (93.7% success rate in patients <2 kg). Long-term outcomes and late adverse event rates are not currently known because this is a relatively new treatment option. Reported complications are rare and include device embolization/malposition, vascular trauma, incomplete closure of the PDA, vascular obstruction (eg, left pulmonary artery or descending aorta), blood loss requiring transfusion, and death. In a recent review of PDA closure in low-weight infants, Pavlek et al outlined areas for future research. (6)

The correct response is C. The video shows PDA closure with a Medtronic (Minneapolis, MN) microvascular plug device. The catheter is in the PDA and the device is released from the delivery cable with stable positioning.

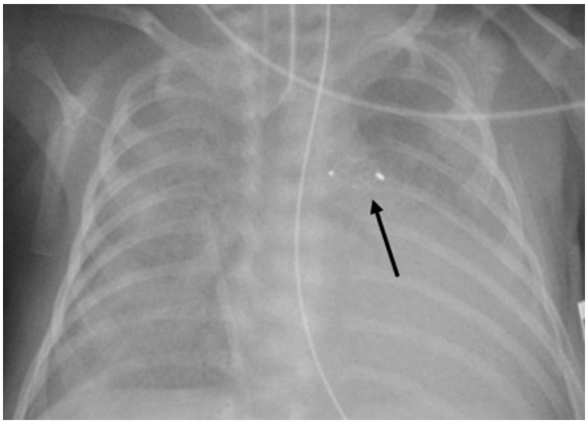


Figure 4. Chest radiograph showing the patent ductus arteriosus closure device (Nitinol metal frame with polytetrafluoroethylene membrane covering and proximal/distal radiopaque markers).

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- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for a preterm neonate with a patent ductus arteriosus.

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Old Problem, New Solution

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Complete Heart Block Masquerading as a Reactive Nonstress Test

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min

AUTHOR DISCLOSURE Drs Rugino and Tien have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. Arterial Umbilical Cord Gas Values

	pH	P_{CO_2} (mm Hg)	P_{O_2} (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤−10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤−10
Metabolic acidosis	<7.20	<60	Variable	≥−10
Mixed acidosis	<7.20	>60	Variable	≥−10

Normal ranges from Obstet Gynecol Clin North Am. *1999;26:695.*

- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:
  - Absent: Amplitude range is undetectable
  - Minimal: Amplitude range is greater than undetectable to 5 beats/min
  - Moderate: Amplitude range is 6–25 beats/min
  - Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions

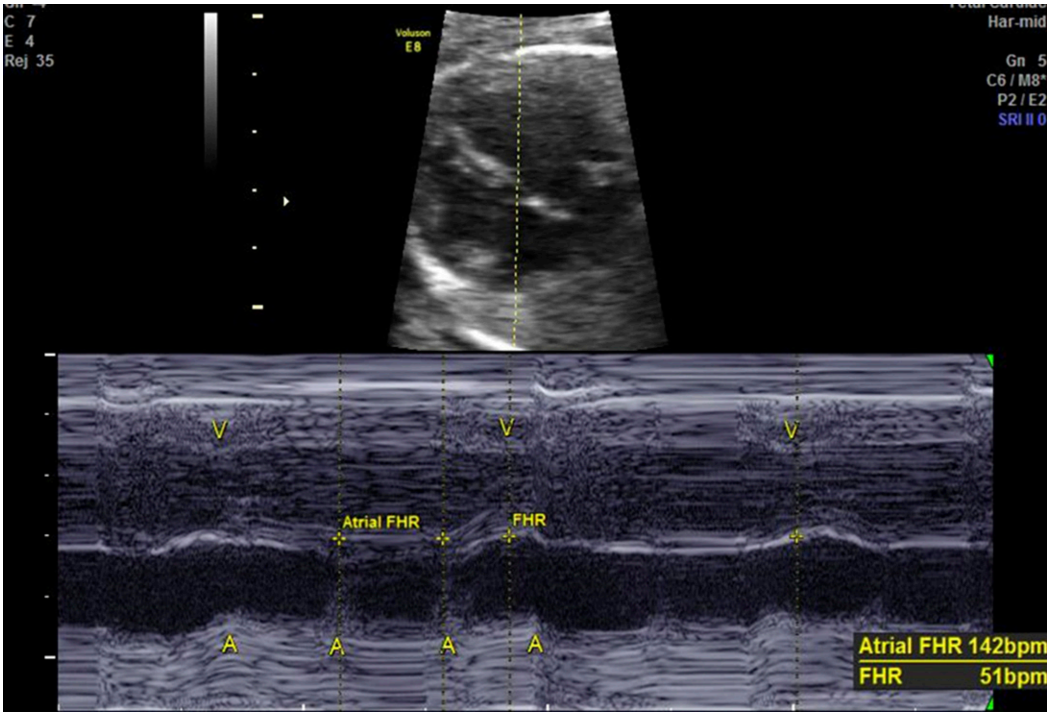

Figure 1. Discordant atrial (A) and ventricular (V) rates in complete congenital heart block. The atrial fetal heart rate (FHR) is 142 beats/min and the ventricular FHR is 51 beats/min when viewed on ultrasonography.

- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
    - Normal: ≤5 contractions in 10 minutes
    - Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
    - Baseline rate: 110 to 160 beats/min
    - Baseline FHR variability: Moderate
    - Late or variable decelerations: Absent

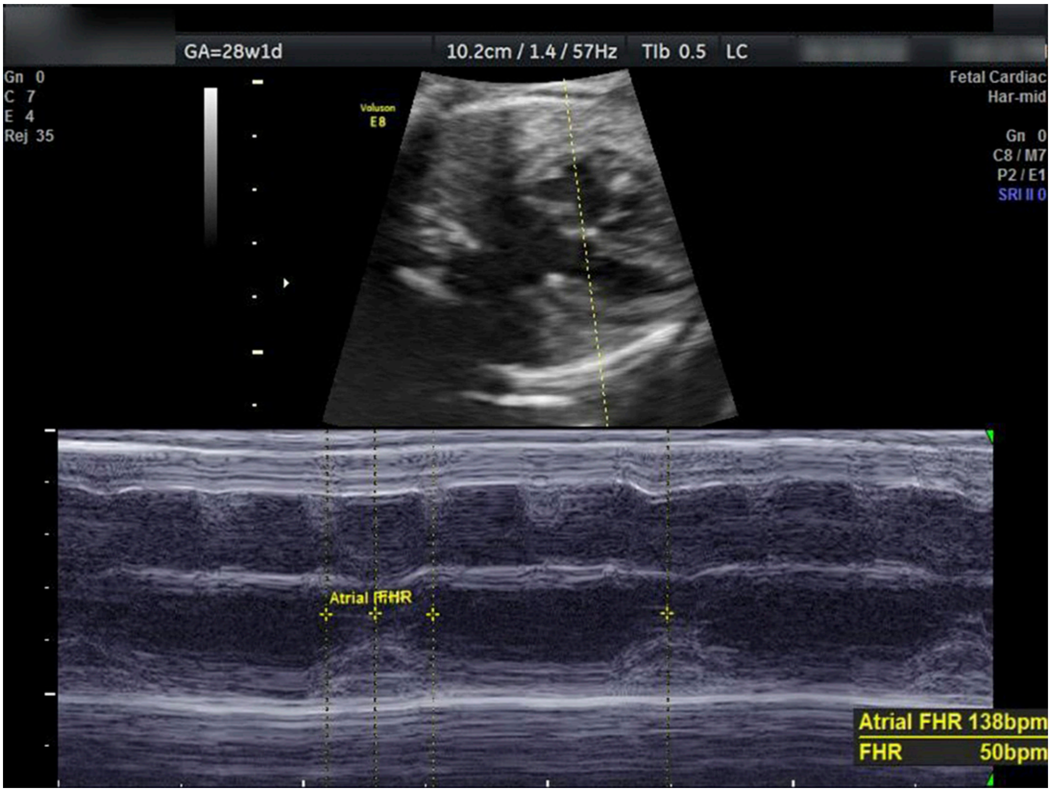

Figure 2. In this M-mode image, the atrial fetal heart rate (FHR) is seen at 138 beats/min and the ventricular FHR at 50 beats/min.

    - Early decelerations: Present or absent
    - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
    - Bradycardia not accompanied by absent variability
    - Tachycardia
    - Minimal or marked baseline variability
    - Absent variability without recurrent decelerations
    - Absence of induced accelerations after fetal stimulation
    - Recurrent variable decelerations with minimal or moderate variability
    - Prolonged decelerations
    - Recurrent late decelerations with moderate variability
    - Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
    - Absent variability with any of the following:
        - Recurrent late decelerations
        - Recurrent variable decelerations
        - Bradycardia
    - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

THE CASE

A 35-year-old gravida 3, para 0-0-2-0 pregnant woman presented at 27 weeks, 5 days of gestation as a late transfer to the maternal-fetal medicine department secondary to a fetal arrhythmia. She had previously received care in another country, and fetal bradycardia had been observed since 22 weeks of pregnancy. She had had 2 prior first-trimester pregnancy losses and an otherwise unremarkable medical history. There was no history of consanguinity and no pertinent family history. She had a risk-reducing quadruple screen and negative screen for anti-SSA/Ro and anti-SSB/La antibodies. She was otherwise feeling well with no concerns for recent infection. She had declined diagnostic testing and had a normal anatomic scan at her initial visit to the maternal-fetal medicine department.

Initial fetal echocardiography performed by pediatric cardiology demonstrated fetal bradycardia with atrial rates in the 130 to 140 beats/min range and ventricular rates around 50 beats/min (Figs 1 and 2), suggestive of complete heart block, with otherwise normal cardiac anatomy and function.

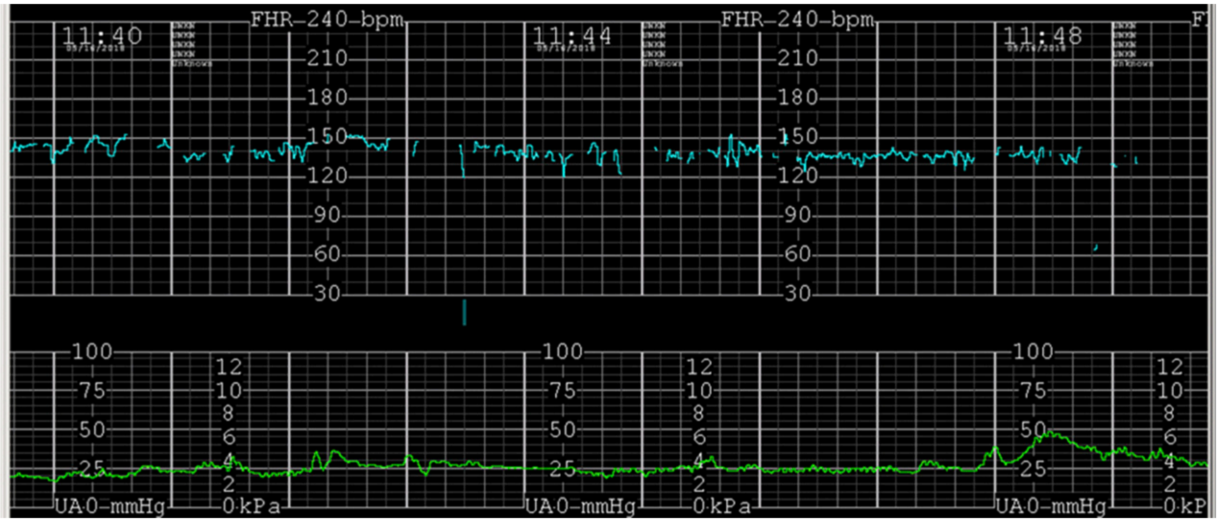

Figure 3. Electronic fetal monitoring strip 1.

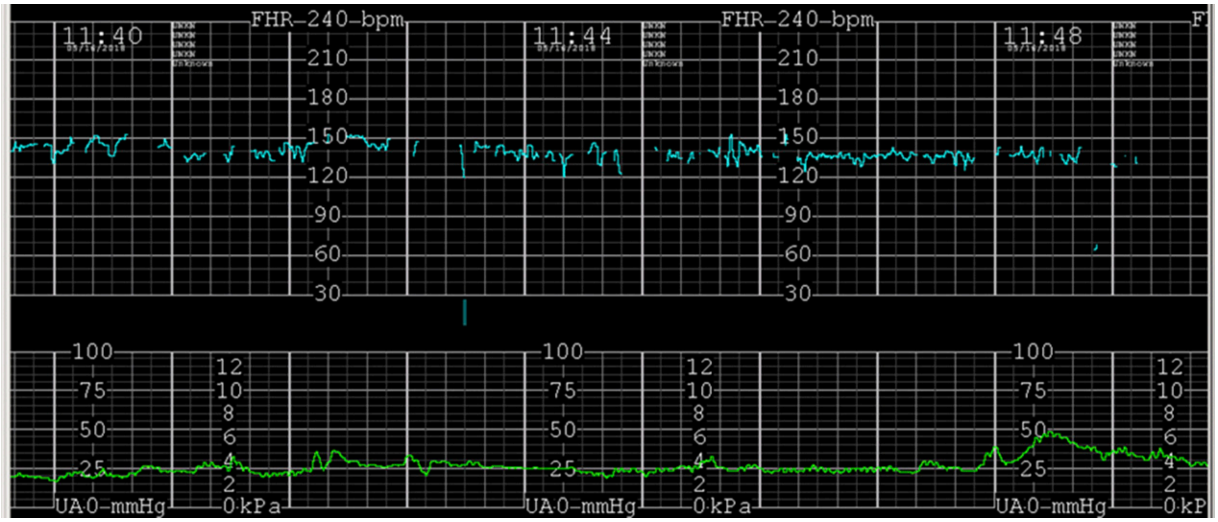

Figure 3. Electronic fetal monitoring strip 1.

Findings on electronic fetal monitoring strip 1 are as follows.

- Variability: Moderate
- Baseline rate: 135 beats/min
- Episodic pattern: 15×15 acceleration
- Periodic pattern: None
- Uterine contractions: Once, not appreciated by the patient
- Interpretation: Category 1, normal tracing, predictive of normal acid-base status
- Differential diagnosis: Normal acid-base status
- Action: Ultrasonography was performed, given the discontinuous tracing and fetal bradycardia previously seen on fetal echocardiography

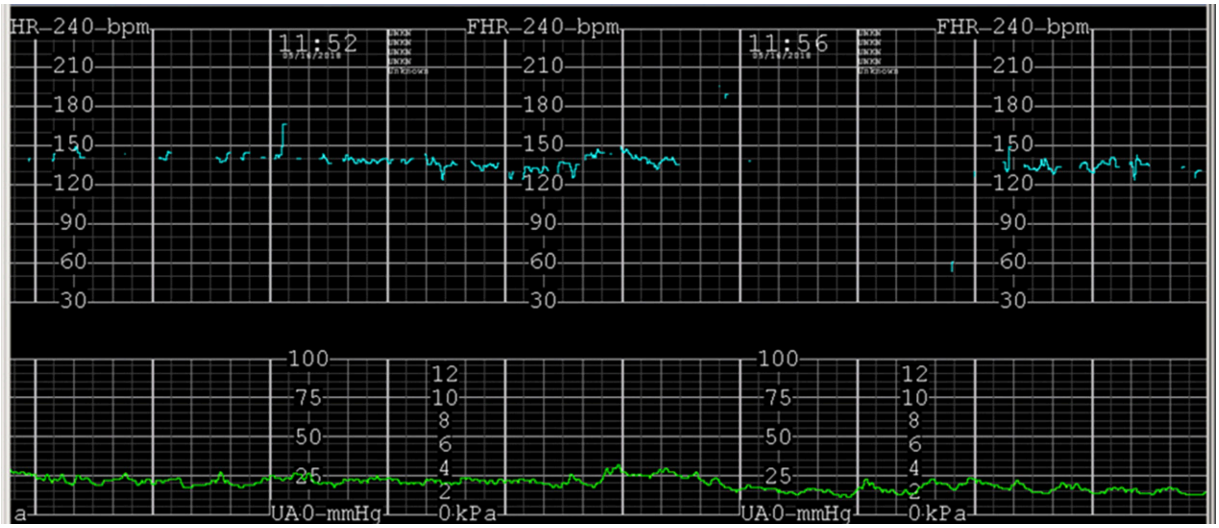

Figure 4. Electronic fetal monitoring strip 2.

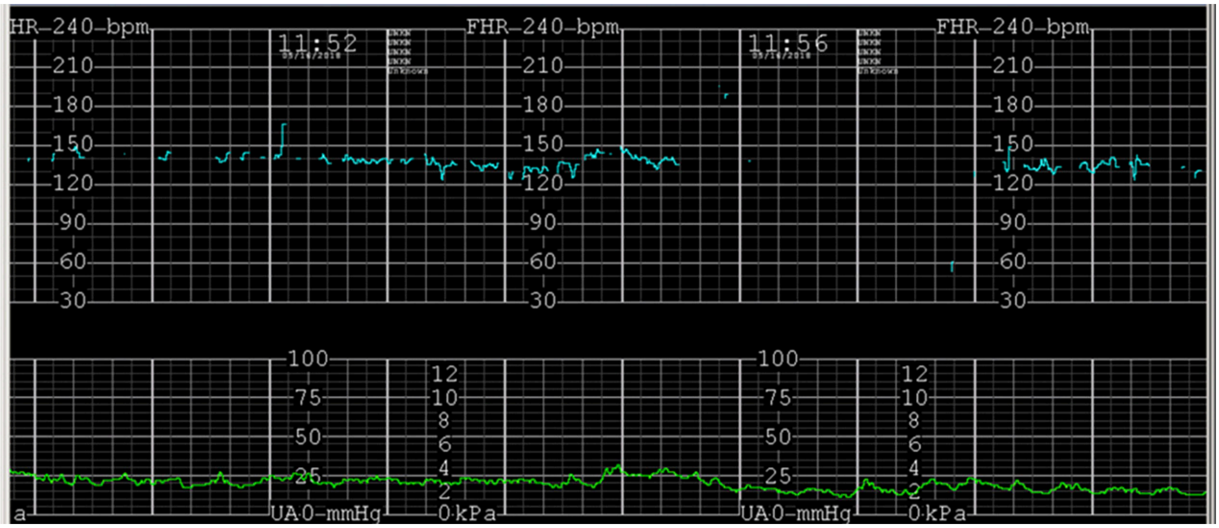

Figure 4. Electronic fetal monitoring strip 2.

Findings on EFM strip 2 are as follows.

- Variability: Moderate
- Baseline rate: 135 beats/min
- Episodic pattern: 10×10 acceleration
- Periodic pattern: None
- Uterine contractions: None, though uterine irritability observed
- Interpretation: Category 1, normal tracing, predictive of normal acid-base status
- Differential diagnosis: Normal acid-base status
- Action: Ultrasonography was performed because of discontinuous tracing and fetal bradycardia previously seen on fetal echocardiography

No evidence of effusion or hydrops was noted. Nonstress tests demonstrated traced FHRs of 130 seconds (Figs 3 and 4), with ultrasonography subsequently demonstrating an atrial rate of 130 beats/min and a ventricular rate of 50 beats/min. Given the discrepancy, it appeared that the nonstress tests had traced the atrial rates in isolation and had not detected the ventricular rates. The patient underwent fetal magnetocardiography for a further detailed evaluation, which confirmed the diagnosis of complete (third-degree) heart block. The patient started treatment with terbutaline 2.5 mg every 6 hours in an attempt to increase the FHR. She tolerated the medication well, and at 29 weeks, her dose was increased to 5 mg twice a day every other day with 2.5 mg twice a day on the alternating days.

Given the challenge of interpreting nonstress tests that traced the atrial rate in isolation, antenatal surveillance was initiated with twice-weekly fetal echocardiography and weekly biophysical profiles. Subsequent fetal echocardiography demonstrated ventricular rates of 53 to 61 beats/min and atrial rates of 150 beats/min without evidence of hydrops.

The patient did well until 32 weeks, 3 days of gestation when she developed swelling, and after evaluation in the labor and delivery department, was diagnosed as having preeclampsia with severe features. She required multiple doses of intravenous antihypertensive medication and treatment was initiated with nifedipine. The patient was given a course of betamethasone for fetal benefit. After initial stabilization, given the unpredictable course of preeclampsia with severe features, as well as the need for delivery in close proximity to a cardiac intensive care unit with neonatal, cardiovascular, and electrophysiology services, the decision was made to transfer her to an institution with these services. The patient was transferred and subsequently had a cesarean delivery at 33 weeks, 1 day of gestation for worsening maternal preeclampsia. At the time of this writing, the infant was in the NICU with complete heart block and being evaluated for placement of a permanent pacemaker.

DISCUSSION

Fetal congenital heart block (also known as *complete heart block* [CHB], *third-degree heart block*, or *complete AV block*) affects approximately 1 in 15,000 to 20,000 newborns at delivery. (1)(2) Approximately 5% of all newborns with CHB have an affected sibling, and 18% of parents have a second affected child. (1)(3) CHB can be congenital, a sequelae of infection, or occur in association with cardiac ischemia or myopathies, autoimmune or endocrine processes. (4) More than half of all congenital CHB cases are associated with structural heart disease. (5) Of the cases without structural defects, approximately 95% are associated with anti-SSA/Ro antibodies, though circulating anti-SSA/Ro antibodies alone have not been shown to be sufficient in causing the disease. (1) Anti-SSA/Ro and SSB/La ribonucleoprotein complex has been associated with the development of congenital heart block likely secondary to tissue injury, (6)(7) which can occur with transplacental passage of maternal immunoglobulin G antibodies in affected women. (6) This may be apparent in utero or even as late as 9 years of age. (6) These antibodies may be present in women with systemic lupus erythematosus or Sjogren syndrome and also in women without symptoms of autoimmune disease. (6)

Congenital CHB without a structural cardiac defect is associated with atrioventricular (AV) node abnormalities, most commonly an absent AV node (ie, atrial-axis discontinuity) or atrionodal discontinuity with fibrous and adipose tissue at the anticipated area of the AV node. (1) AV nodal dysfunction or absence contributes to independently paced atrial contractions and ventricular contractions resulting in a decreased ventricular rate. In the fetus, this dysfunction can lead to chronic fetal bradycardia with ventricular rates as low as the 50 beats/min. (8)

The first description of congenital complete heart block in the fetus was reported in 1945. (9) With increasing use of routine FHR monitoring and ultrasonography, congenital CHB is being diagnosed prenatally with increasing frequency. (1) Fetal heart block may be detected as early 16 weeks' gestation, with detection most frequently between 20 and 24 weeks of pregnancy. (3) Infants with an antenatal diagnosis may have improved outcomes compared with infants diagnosed after delivery. (2)

CHB is essentially irreversible. (3)(7) Studies have suggested that prolonging pregnancy with frequent monitoring may lead to better outcomes compared with the morbidity associated with iatrogenic prematurity. If suspected, fetal echocardiography has been suggested as the method of choice for the detection, analysis, and follow-up of fetal arrhythmias throughout pregnancy. (3)

Treatment recommendations and success are largely anecdotal in the absence of controlled clinical trials. (2) Suggested antenatal treatment of congenital CHB has included beta sympathomimetics to increase FHR, plasmapheresis, and steroids to target the antibody-mediated and inflammatory component. In the PR Interval and Dexamethasone Evaluation (PRIDE) study evaluating the use of dexamethasone in fetuses with anti-SSA/Ro antibodies and newly diagnosed CHB, 30 pregnant women were given dexamethasone (22 with fetal third-degree block and the others with fetal first- or second-degree block) and 10 women were not treated (9 with fetal third-degree block). Results demonstrated no reversal of fetal third-degree block observed in the treated group. Pacemaker use at birth and 1 year of age were comparable between the 2 groups. A potential benefit of dexamethasone treatment may have been noted in fetuses with first- or second-degree block; however, dexamethasone did not appear to affect progression of second-degree to third-degree heart block. (7) Similarly, in a recent meta-analysis including studies with 162 fetuses with immune-mediated CHB treated with steroids, there was no difference in the rate of regression (3.0% vs 4.3% not treated; odds ratio [OR] 0.9; 95% confidence interval [CI] 0.1–15.1), pacemaker requirement at birth (71.5% of fetuses treated and 57.8% of those not treated; OR 9; 95% CI 0.4–3.4), and overall mortality. (10) The use of digoxin or furosemide to treat associated ventricular dysfunction and hydrops, if present, has also been described. (7) Atropine has been suggested to increase atrial rate in cases of fetal heart block, but it does not appear to lead to improved ventricular rate. (1)

During labor, a fetal scalp electrode should be used for intrapartum monitoring if membranes have ruptured, because external fetal monitoring may be difficult to establish and maintain. (1) If the fetus has heart failure, hydrops, or a ventricular rate less than 55 beats/min, cesarean section may be considered because of the high likelihood of fetal intolerance during labor. (1)(9) Cesarean section may also allow for a timed delivery to assist in the coordination of postnatal multidisciplinary care. In the absence of heart failure or signs of fetal compromise, vaginal delivery may be attempted. (1)(9) Ex utero intrapartum treatment for ventricular pacing has also been described for CHB. (11)

Increased atrial and ventricular rates may lead to better outcomes after delivery. Neonatal death, when it occurs, most often results secondary to ventricular fibrillation arrest, pulmonary hypertension, and refractory heart failure. (2) Isoproterenol and temporary pacing need to be available postnatally in the delivery room and at the bedside in case emergent acceleration of the ventricular rate is needed. (12) A low ventricular rate appears to be associated with poor outcomes. In a series of 6 fetuses with CHB diagnosed at 20 to 30 weeks' gestation, ventricular rate was observed to decrease as the pregnancies progressed (60 vs 51 beats/min), with cardiac decompensation observed in 2 fetuses with ventricular rates less than 55 beats/min. (13) Three patients had treatment with digoxin and sympathomimetic medication, and all newborns required pacemakers. At 2 weeks of age, the infants had tricuspid regurgitation, with 2 of 5 surviving infants having no symptoms at 1 year of age. One infant had neonatal lupus, 2 had a persistent patent ductus arteriosus, and 1 developed cardiomyopathy. (13)

Typically, indications for postnatal pacing include the following.

- Congestive heart failure
- Ventricular rate less than 55 beats/min in isolated AV nodal block or less than 65 beats/min when associated with heart disease
- Presence of prolonged QTc (>0.50 seconds)
- Stokes-Adams attacks (loss of consciousness secondary to periods of slow or absent pulse in the setting of an abnormal heart rhythm)
- Frequent ventricular ectopic beats or alternating ventricular pacemakers (3)(9)

Congestive cardiac failure has been demonstrated when the ventricular rate is consistently less than 55 beats/min; therefore, pacing may be necessary to improve outcomes in these newborns. (12)(13) Immediate postpartum pacing following a planned delivery at a tertiary care center has demonstrated improved outcomes in cases of congenital CHB (2); however, dependency on permanent pacing carries the potential for significant morbidity. (3) In cases without immediate postdelivery pacing, most infants required pacing within 1 month after birth. (3)

Not surprisingly, CHB associated with structural heart disease portends a grim prognosis, with mortality rates from 80% to 100% (14) compared with mortality rates of 8% to 11% in cases of fetal CHB without structural heart disease. (3) Severe cardiomegaly is a significant poor prognostic indicator. (15) A recent review examined 127 patients (63 diagnosed prenatally) with CHB including both immune and nonimmune (anti-SSA-Ro/SSB-La antibody-exposed and unexposed) cases with pacemaker placement. The median age of pacemaker placement was 3.2 years with a median follow-up of 8.7 years. Nine patients had left ventricular dysfunction and 4 had died. Not surprisingly, left ventricular dysfunction was associated with earlier diagnosis (prior to 1 month of age), as well as abnormal ventricular function before pacemaker placement. (16)

Care and management of a fetus with congenital CHB should include a detailed anatomic and cardiac structural survey to assess for coexisting anomalies. Genetic testing should be discussed and offered, as well as evaluation for potential immune-mediated causes (anti-SSA/SSB antibodies). Antenatal care should include comanagement with maternal-fetal medicine, pediatric cardiology, and consultation with cardiovascular surgery and electrophysiology. Antenatal surveillance should include serial evaluation of cardiac function as well as ultrasonographic screening for developing fetal hydrops. Nonstress tests can be challenging to interpret, as was the case for the current patient because of isolated atrial FHR tracing on EFM; thus ultrasonographic biophysical profiles are a reasonable surrogate for surveillance. Terbutaline may be considered to increase FHR with monitoring of maternal symptoms. Cesarean section may be required if fetal well-being cannot be ensured during labor. Delivery should be at a center with neonatology, cardiac surgery, cardiac intensive care unit, and electrophysiology capabilities.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know appropriate management of common arrhythmias in the fetus and newborn infant, and understand the potential complications or adverse effects of approaches and drugs used.

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Strip of the Month: Complete Heart Block Masquerading as a Reactive Nonstress Test

Angela Rugino and Shelly Tien

NeoReviews 2018;19;e698
DOI: 10.1542/neo.19-11-e698

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Newborn with Enlarged Head, Narrow Thorax, and Short Limbs

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THE CASE

A term newborn with macrocephaly, a narrow bell-shaped thorax, and micromelia.

Prenatal and Birth Histories

- Born to a 36-year-old gravida 5, para 3 African American woman with 3 living children.
- Prenatal history was significant for maternal chronic hypertension, polyhydramnios, and fetal skeletal dysplasia diagnosed on ultrasonography during the second trimester.
- The woman was followed by a perinatologist. Prenatal counseling was provided; the woman declined amniocentesis and requested neonatal resuscitation and postnatal genetic testing/confirmation.
- Prenatal laboratory findings: Group B *Streptococcus* status: unknown; hepatitis B surface antigen: negative; human immunodeficiency virus: negative; rapid plasma reagent (RPR): reactive (history of adequate treatment, RPR profile not indicative of recurrence or transmission to infant); rubella: immune.
- No history of skeletal dysplasia in the family.
- The woman presented in preterm labor at an estimated gestational age of 31 weeks; the infant was delivered via repeat cesarean section.
- The infant was born nonvigorous; received positive pressure ventilation and intubation for absence of respiratory effort in the delivery room. Apgar scores were 3, 5, and 7 at 1, 5, and 10 minutes, respectively.

Presentation

The infant had multiple congenital anomalies including frontal bossing, macrocephaly, shortened extremities with skin folds, and a narrow, bell-shaped thorax. Parents were counseled regarding the infant's poor prognosis and futility of care, in view of the clinical presentation. The parents requested resuscitation and further testing. The infant was admitted to the NICU and placed on high-frequency oscillatory ventilation with a mean airway pressure of 14 cm H_2O and fraction of inspired oxygen concentration (FiO_2) of 1; confirmatory tests were performed based on phenotypic presentation.

PROGRESSION

Vital Signs

- Heart rate: 164 beats/min
- Respiratory rate: 74 breaths/min
- Blood pressure: 54/22 mm Hg (mean 37 mm Hg)

AUTHOR DISCLOSURE Drs Khan and Manzar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

- Oxygen saturation: 92% ($FiO_2 = 0.40$)
- Temperature: 98.2°F (36.8°C)

Physical Examination

- Birthweight: 1.963 kg (82nd percentile); length: 35 cm (<3rd percentile); head circumference: 38 cm (>95th percentile)
- Head: Macrocrocephaly; frontal bossing; large anterior fontanelle; midface hypoplasia with depressed nasal bridge; patent nares
- Oral cavity: Pink mucosa, intact palate, no lymphadenopathy
- Lungs: Bell-shaped chest; small thorax; fair air exchange; moderate bilateral intercostal and subcostal retractions
- Cardiovascular: Normal S1, S2; regular rate and rhythm; no murmurs or gallops
- Abdomen: Soft, protuberant abdomen; 3-vessel cord; no organomegaly; hypoactive bowel sounds
- Genitourinary: Normal male genitalia; patent anus
- Skeletal: Bilateral shortened extremities
- Skin: Redundant skin folds along shortened extremities
- Neurologic: Moderate generalized hypotonia

Laboratory Studies

- Cord blood gas: pH: 7.29; Pco_2: 51 mm Hg; base deficit: −2.0 mmol/L; Po_2 <30.3 mm Hg
- White blood cell count: $8.8 \times 10^3/\mu L$ ($8.8 \times 10^9/L$) with 16% neutrophils, 75% lymphocytes
- Hemoglobin: 15.9 g/dL (159 g/L)
- Platelet count: $215 \times 10^3/\mu L$ ($215 \times 10^9/L$)
- Sodium: 130 mEq/L (130 mmol/L)
- Calcium: 8.7 mg/dL (2.1 mmol/L)
- Phosphorus: 6.5 mg/dL (2.1 mmol/L)
- Alkaline phosphatase: 79 U/L (1.3 μkat/L)
- Postnatal blood gas (within first hour after birth): pH: 7.24, $Paco_2$: 51 mm Hg (6.8 kPa); Pao_2: 99.6 mm Hg (13.2 kPa); bicarbonate: 17.4 mEq/L (17.4 mmol/L); base deficit: −6.0 mmol/L; FiO_2: 1
- Blood culture: Negative
- RPR: Nonreactive

Imaging Studies

- Skeletal survey: Proximal long bones are short with flared, irregular metaphyses. Brachydactyly is also evident. The chest is narrow and bell-shaped. Spinal column with flat vertebrae (platyspondyly) (Fig 1).
- Cross table lateral skull radiograph showing macrocephaly with frontal bossing (Fig 2).
- Axial view T1-weighted magnetic resonance imaging (MRI) scan of the brain with absent corpus callosum, enlarged third ventricle and cortical thinning (Fig 3).
- MRI scan of the brain, T1-weighted, sagittal view showing absent corpus callosum, frontal bossing, enlarged ventricles, and small base of skull with narrowed foramen magnum (Fig 4).
- Cranial MRI, T2-weighted axial view showing dysplastic temporal lobe with deep transverse temporal sulci on the inferomedial surface (abnormal development, mediated by constitutive activation of fibroblast growth factor receptor 3 [FGFR3] protein) (Fig 5).

DIFFERENTIAL DIAGNOSES

- Achondrogenesis
- Asphyxiating thoracic dystrophy (Jeune thoracic dystrophy)
- Campomelic dysplasia
- Fibrochondrogenesis
- Hypophosphatasia congenita
- Osteogenesis imperfecta type II
- Rhizomelic chondroplasia punctata
- Short rib polydactyly syndromes
- Thanatophoric dysplasia

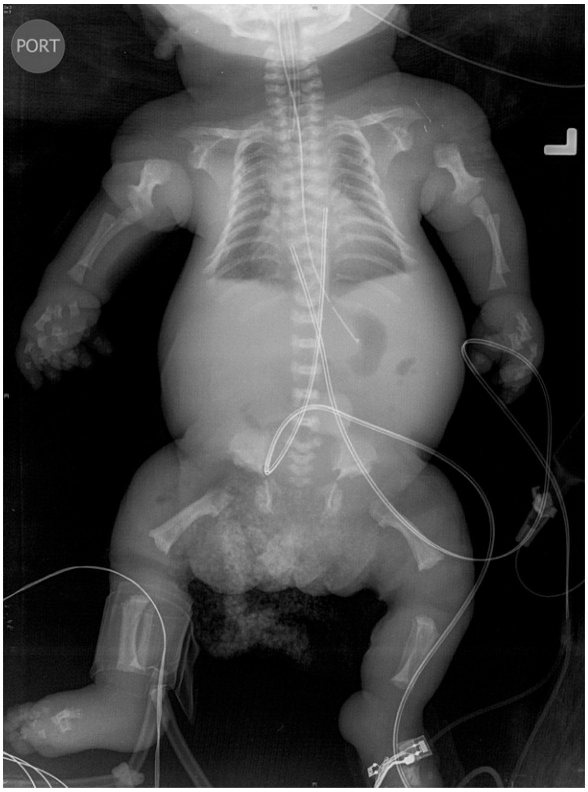

Figure 1. Skeletal survey. Proximal long bones are short with flared, irregular metaphyses. Brachydactyly is also present. The chest is narrow and bell-shaped. Spinal column has flat vertebrae (platyspondyly).

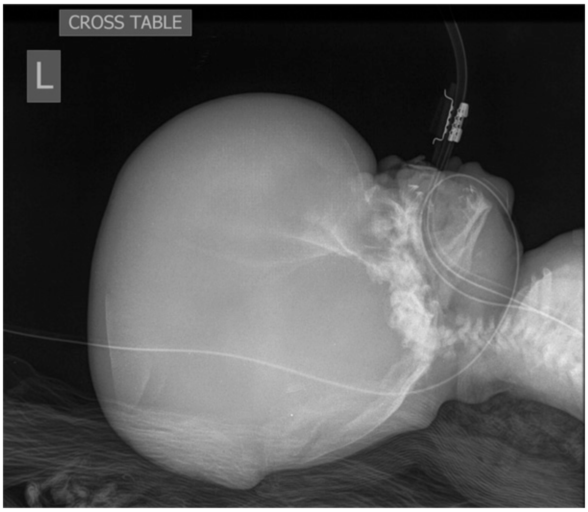

Figure 2. Cross table lateral skull radiograph showing macrocephaly with frontal bossing.

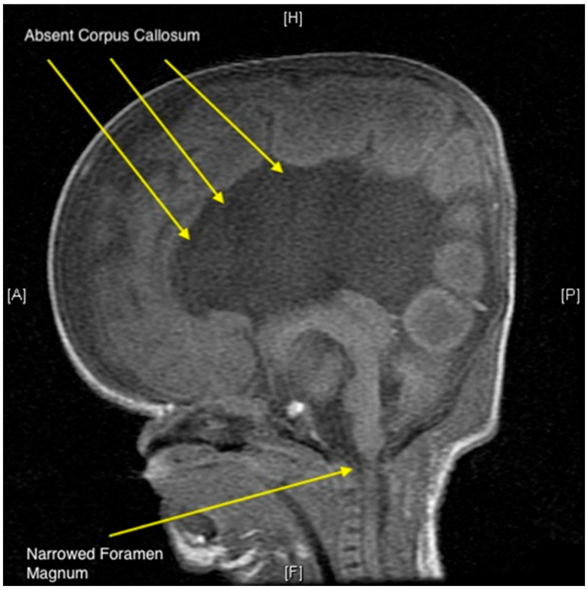

Figure 4. Magnetic resonance imaging scan of the brain, T1-weighted, sagittal view showing absent corpus callosum, frontal bossing, enlarged third ventricle, small base of skull with narrowed foramen magnum.

ACTUAL DIAGNOSIS

Thanatophoric dysplasia type II

Diagnosis of thanatophoric dysplasia (TD) in this patient was confirmed with 13-mutation testing for TD, types 1 and 2 (FGFR3). The polymerase chain reaction and fluorescence resonance energy transfer for variants in the *FGFR3* gene was positive for 1 mutation in the *FGFR3* gene, consistent with the diagnosis of TD type 2 (TD2). Once the diagnosis was confirmed, the family was counseled again regarding the futility of care; in discussions with the medical team, the decision was made to withdraw life-sustaining support on day 8 of age. The infant was provided comfort care and died soon after withdrawal of medical treatment.

What the Experts Say

The term thanatophoric is Greek for "death bearing." TD is the most common lethal skeletal dysplasia in the perinatal

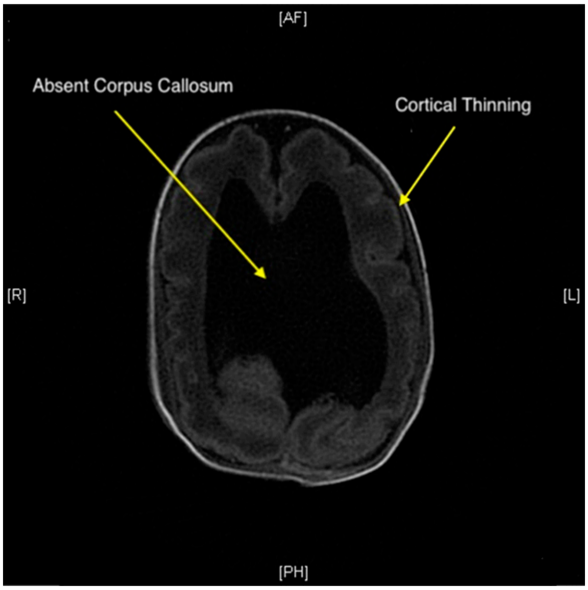

Figure 3. Axial view T1-weighted magnetic resonance imaging scan of the brain with absent corpus callosum, enlarged ventricles, and cortical thinning.

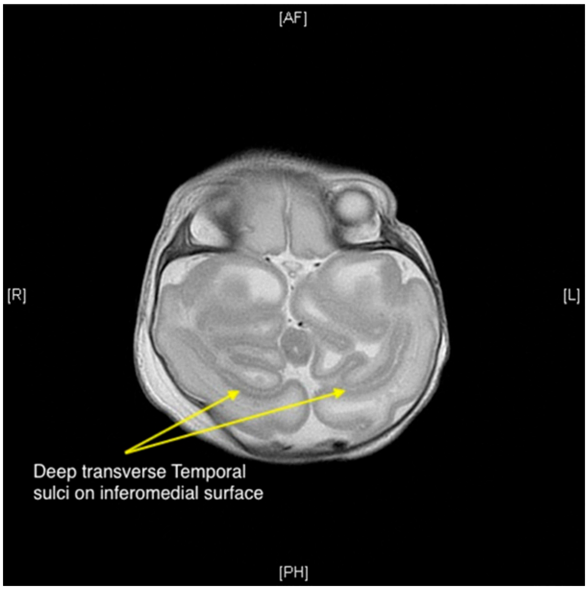

Figure 5. Cranial magnetic resonance imaging scan, T2-weighted axial view showing dysplastic temporal lobe with deep transverse temporal sulci on the inferomedial surface (associated with abnormal development, mediated by constitutive activation of FGFR3 protein).

period with a reported incidence of 1 in 20,000 to 1 in 50,000 births. (1)(2) Respiratory failure is the primary cause of postnatal death. Case reports have described survival into childhood with extensive support. (3)(4)

TD is an autosomal dominant genetic disorder caused by de novo mutations in the *FGFR3* gene. The *FGFR3* gene encodes instructions for making the FGFR3 protein. Part of a family of 4 proteins, this receptor is involved in cascades of intracellular reactions that regulate tissue growth and differentiation. Gene mutations trigger the FGFR3 protein to be overly active, which leads to the developmental disturbances of tissue growth and differentiation that are characteristic of TD, including that of bone and brain tissue.

TD is characterized by:

- Macrocephaly or a cloverleaf skull deformity with frontal bossing
- Prominent wide-spaced eyes
- A flat facies
- Micromelia with rhizomelic predominance (proximal limb shortening) and brachydactyly, a normal trunk length, and normal bone mineralization without fractures
- Redundant skin folds along the extremities
- A small thoracic circumference with short ribs
- Underdeveloped lungs
- Hypotonia
- Platyspondyly (flattened vertebral bodies)

The most characteristic brain abnormalities include temporal lobe dysplasia with deep and transverse temporal sulci across the inferomedial surface (as demonstrated in this report). In a review of autopsies performed on TD cases, 100% of cases on which autopsies were performed had temporal lobe dysplasia. (5) Other associated brain abnormalities include hippocampal dysplasia (as was identified in our case) and polymicrogyria. (6) Polyhydramnios is present in approximately 50% of affected pregnancies.

Two major forms of TD have been described.

TD1 is the more common form of TD. At least 12 *FGFR3* gene mutations that substitute a single amino acid in the FGFR3 protein have been found to cause TD1. The most common mutations are the R248C mutation (cysteine replaces arginine at FGFR3 protein position 248) and the Y373C mutation (cysteine replaces tyrosine at FGFR3 protein position 373) in the *FGFR3* gene. TD1 is characterized by the typical bowed (“French telephone receiver”) shape of the femur and uncommonly the cloverleaf skull deformity.

TD2 is usually caused by the K650E mutation in the *FGFR3* gene (glutamic acid replaces lysine at FGFR3 protein position 650). TD2 is typically associated with straight femurs with flared metaphyses and the cloverleaf skull (a trilobed appearance of the skull in the coronal plane that results from premature craniosynostosis of the lambdoid and coronal sutures).

The diagnosis of TD is based on findings on clinical examination, prenatal imaging studies, and/or testing for the *FGFR3* gene mutation. Molecular genetic testing is able to detect up to 99% of the gene mutations.

The prognosis for patients affected with TD is poor, with perinatal death occurring secondary to pulmonary hypoplasia and/or brainstem compression. The primary management of live-born infants is the provision of comfort care. Palliative care can be offered to families. Newborns may require extensive supportive measures to survive, including tracheostomy for prolonged ventilation, seizure management, shunt placement for hydrocephalus, and surgical decompression for relief of craniocervical junction constriction.

Although similarities exist in phenotypic presentations of skeletal dysplasias, there are some differentiating features. TD is associated with normal bone mineralization, no fractures, macrocephaly, short limbs with rhizomelic predominance, and normal trunk length. Achondrogenesis is associated with patchy demineralization, most pronounced in the vertebral bodies, ischium, and pubic bones, associated occasionally with fractures and a short trunk length. Asphyxiating thoracic dystrophy is characterized by a narrow thorax with short ribs leading to progressive respiratory insufficiency over the first few months of age, short limbs with acromelic predominance (distal segment shortening), and sometimes polydactyly. Campomelic dysplasia is associated with a mildly narrow thorax, hypoplastic scapula, and cervical vertebrae (63% of cases), congenital heart disease (33% of cases), and facial abnormalities. Fibrochondrogenesis is a rare lethal osteochondroplasia with an autosomal recessive mode of inheritance. It is associated with a normal cranial size, decreased mineralization of the skull, and vertebral platyspondyly with midline clefts. The bones have irregular metaphyses with peripheral spurs and extra-articular calcifications, giving the appearance of stippling. Hypophosphatasia congenita is associated with severe micromelia, a small thoracic circumference, patchy or generalized demineralization, occasional fractures, a normal cranial size, and a normal trunk length. Osteogenesis imperfecta type II is associated with generalized demineralization of the bones with fractures, lack of macrocephaly, and a short trunk. Rhizomelic chondroplasia punctata is associated with rhizomelic micromelia, enlarged epiphyses with characteristic stippling, joint contractures, and coronal clefting of the vertebral bodies. Short rib polydactyly syndrome is associated with severe micromelia, small thoracic circumference, normal cranial size, and polydactyly. (7)

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features and know how to diagnose and manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodermal dysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc.
- Know the familial/genetic features of neurologic disorders associated with increased head circumference.

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Suggested Reading

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ANSWER KEY FOR NOVEMBER 2018 NEOREVIEWS

Enteral Feeding of the Preterm Infant: 1. D; 2. A; 3. C; 4. E; 5. B.

Probiotics, Prebiotics, and Synbiotics for Preterm Neonates: 1. C; 2. A; 3. C; 4. D; 5. D.

Newborn with Enlarged Head, Narrow Thorax, and Short Limbs

Liaqat Hayat Khan and Shabih Manzar

NeoReviews 2018;19;e707
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Vol. 19 No. 12 December 2018

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Answer Key appears on page e786.

Hypothermic Neuroprotection for Neonatal Encephalopathy in Low- and Middle-Income Countries: A New Approach to an Old Problem

Paolo Montaldo, MD,* Peter J. Lally, PhD,* Vânia Oliveira, MSc,* Sudhin Thayyil, MD, PhD*

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Abstract

Little progress has been made over the past decade in improving the outcomes of infants with neonatal encephalopathy in low- and middle-income countries (LMICs), and millions of infants still die or sustain permanent neurodisability every year. One of the key reasons for this lack of progress is a disconnect between encephalopathy research in high-income countries and LMICs. The majority of the neonatal encephalopathy research has been conducted in high-income countries with a low disease burden, without the involvement of LMICs. Here we discuss how a collaborative approach—particularly between middle-income countries and high-income countries—enables the use of state-of-the-art magnetic resonance biomarkers and host gene expression profiling for effective disease stratification. Using the example of the Hypothermia for Encephalopathy in Low- and middle-Income countries (HELIX) trial, we describe how this approach may result in a paradigm shift in global perinatal brain research over the next decade.

AUTHOR DISCLOSURE Drs Montaldo, Lally, and Thayyil and Ms Oliveira have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ACT	Antenatal Corticosteroids Trial
CI	confidence interval
FEAST	Fluid Expansion as Supportive Therapy
LMICs	low- and middle-income countries
MR	magnetic resonance
NE	neonatal encephalopathy
PCM	phase-changing material
RR	relative risk

BACKGROUND

Every year, approximately 1 million infants die, and many more sustain lifelong disabilities because of neonatal encephalopathy (NE), particularly in low- and middle-income countries (LMICs), which bear 99% of the encephalopathy burden, with rates of 10 to 20 cases per 1,000 live births. (1)

In the past decade, several randomized controlled trials in high-income countries have shown that after NE, therapeutic hypothermia reduces death (typical relative risk [RR] 0.75; 95% confidence interval [CI] 0.64–0.88) (2) and neurodisability at 18 to 24 months (typical RR 0.77; 95% CI 0.63–0.94) and at school age (typical RR 0.59; 95% CI 0.37–0.94). (3)(4) This therapy is now standard care after years of thorough preclinical and clinical research. This also includes the most recent Neonatal Research Network trials, which studied longer (120 hours) or deeper (89.6°F [32°C]) cooling and assessed the effect of therapeutic hypothermia initiated after 6 hours of age. (5)(6)

Since the demonstration of the short- and long-term benefits of therapeutic hypothermia in infants with moderate or severe encephalopathy in high-income countries and its introduction as a standard of care in such settings, clinical and scientific communities worldwide have enquired about the feasibility of therapeutic hypothermia in LMICs. However, despite the simplicity of the intervention and proven benefit, the uptake of therapeutic hypothermia in LMICs is still poor, probably reflecting the conflicting evidence from studies using low-cost technologies and the associated logistical issues. (7) In high-income countries, therapeutic hypothermia is deployed only in tertiary neonatal centers with highly specialized NICU teams and infrastructure. In contrast, LMIC neonatal care can be significantly resource-limited across several aspects and is highly variable. It is also possible that the population differences and comorbidities between these settings may adversely affect the therapeutic efficacy of hypothermia therapy. Moreover, the burden of disease has different implications in low resource settings where the support offered at the community level and by the health-care system is poor.

Although some LMICs have adopted the evidence from high-income countries, either locally or at a national level, and started offering therapeutic hypothermia to infants who suffer from NE, it is important to understand the current evidence and where this therapy has been applied in equivalent settings. (8) The aim of this review is to discuss the current status of therapeutic hypothermia in LMICs and describe a potential way forward, which can lead to a paradigm shift in global perinatal brain research.

THE EVIDENCE FOR THERAPEUTIC HYPOTHERMIA IN LMICs AND THE CURRENT SITUATION

Although numerous pilot studies of therapeutic hypothermia have been conducted in LMICs so far, they have been heterogeneous in their design and the sample sizes have been too small to draw any firm conclusions.

Two pilot randomized controlled trials, one in sub-Saharan Africa and another in India, reported increased mortality in cooled newborns. Robertson et al (9) randomized 36 infants with encephalopathy in Uganda to usual care or whole-body hypothermia using water bottles for 72 hours. Overall, 8 infants died, of whom 7 were in the cooling arm and 1 was in the standard care arm (RR 5; 95% CI 0.69-36.5). This difference was not statistically significant. Blood cultures or blood indices suggestive of infection were not available for any of these patients, and concerns were raised about whether the high perinatal infection rate might have been responsible for the increased mortality. However, a later observational study reported that the incidence of perinatal infections in these settings was no different than that in high-income countries. (10) These authors reported bloodstream-positive sepsis (assessed using blood culture and polymerase chain reaction) in 8.9% (95% CI 5.6%-13.6%) of infants with NE (10) in Uganda, which is surprisingly lower than the bloodstream-positive sepsis rates (17%; 95% CI 14.9%-18.8%) reported from the UK National Cooling Registry. (11)

As part of the Peacock trial (Phase Change Material for Whole Body Cooling in Kerala, India), (12) we randomized 33 infants to whole-body hypothermia using a phase-changing material (PCM; Fig 1)—16 were assigned to usual care and 17 to the cooling arm. This was the first clinical use of the PCM for cooling therapy. Overall, 6 infants died, of whom 4 were in the cooling arm and 2 were in the standard care group (RR 1.88; 95% CI 0.4-8.9). The PCM is typically made of polymers with long chain molecules primarily of carbon and hydrogen, and absorbs and releases thermal energy during the process of melting and freezing. This material has a wide range of applications in the industry and offers a low-cost (approximately $40 per kg of PCM) method for cooling therapy. However, the cooling efficacy of PCM is weak, and requires a low ambient temperature to induce cooling. The temperature control stability is poor, and hence, close nursing monitoring is required to ensure that the core temperature remains within the target range.

In 2013, our research group published a systematic review of the available evidence on the use of therapeutic hypothermia in newborns in LMICs. (13) This review included data from 7 studies and a total of 567 infants

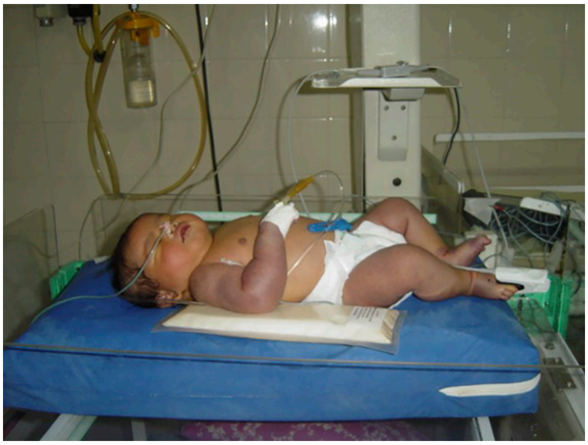

Figure 1. Whole-body cooling using phase-change material. Printed with permission from Roberson NJ, Kendall GS, Thayyil S. Techniques for therapeutic hypothermia during transport and in hospital for perinatal asphyxia encephalopathy. *Semin Fetal Neonatal Med.* 2010;15(5):276-286.

who were offered cooling treatment using various methods such as frozen gel packs, PCM, natural cooling, servo-controlled fans, and others. This meta-analysis showed a reduction in neonatal mortality with cooling, even though this was not statistically significant. (13) However, the CIs were wide (RR 0.74; 95% CI 0.44-1.25) and therefore it was not possible to exclude either a benefit or harm. Most trials had important methodologic flaws such as the lack of standardized follow-up, and in some cases, poor details of the cooling devices used. In particular, in the largest of the trials included, Zhou et al studied the efficacy of selective head cooling in 256 infants in China who were randomized to selective head cooling or usual care. (14) Almost 20% of the infants recruited in this study had mild encephalopathy and infants who were at risk for sepsis were excluded, along with additional postrandomization exclusions.

Since then, other small pilot studies have been undertaken in LMICs. These included 1 case series from South Africa (15) and 3 publications from India, of which 1 was a randomized, controlled trial, (16) 1 was a case series, (17) and 1 was a multicenter, uncontrolled, feasibility study. (18)

The case series in South Africa took place in a tertiary public referral hospital in Cape Town. The authors retrospectively reported outcome data on 99 infants with moderate or severe NE who received whole-body hypothermia from 2008 to 2011. Only 50 traceable survivors were seen at the 1-year follow-up, of whom only 9 (18%) had a significant neurologic impairment. (15)

Gane and colleagues described a randomized, controlled trial at a tertiary care center in India between 2011 and 2013, in which 61 infants each were allocated to whole-body cooling or usual care. (16) Infants in the hypothermia group were cooled using gel packs to achieve a target rectal temperature of 91.4°F to 93.2°F (33°C–34°C). The primary outcome of the trial was based on the oxidative stress-induced DNA damage, whereas a neurodevelopmental assessment at 1 year (Developmental Assessment Scale for Indian Infants II) was considered as a secondary outcome. The study showed that there was less oxidative stress-induced DNA damage and higher motor and mental developmental quotients in the hypothermia group. Authors reported adverse outcome (death or developmental delay at 12 months) in 9 (15.7%) of 57 cooled infants compared with 26 (44.8%) of 58 infants receiving usual care (P=.001). This amounts to a relative risk reduction of 65%, which is much higher than the risk reduction reported in any of the previous cooling trials. Given the poor study quality, lack of masking of the outcome assessments to the allocation, and suboptimal research governance in these settings, the significance of these data is unclear. (16)

Sowjanya and colleagues described a case series of 17 infants with NE who had cooling therapy in south India. None of these infants died in the NICU, but 31% had abnormal neurologic findings at discharge. (17)

More recently, Thomas and colleagues undertook a multicenter, uncontrolled, feasibility study, which involved 11 tertiary neonatal units in India between 2014 and 2015, recruiting 103 infants with perinatal asphyxia. (18) Therapeutic hypothermia was provided using PCM, with a target temperature of 92.3±0.5°F (33.5±0.5°C). The authors reported that the maintenance of the target temperature was comparable to that achieved with standard servo-controlled equipment, though the accuracy of hourly rectal temperature data in this study is questionable.

Although these studies have demonstrated that cooling can be feasible and safe even in less well-resourced settings, none of them were conclusive. These studies were typically single arm studies inadequately powered to investigate clinically relevant outcomes, or they did not include a long-term neurologic follow-up examination. Altogether, therefore, these data cannot provide adequate evidence for either the safety or efficacy of therapeutic hypothermia as a neuroprotective strategy in LMICs.

SHOULD THERAPEUTIC HYPOTHERMIA BE ADOPTED AS STANDARD CARE IN LMICs?

Some researchers and clinicians argue that the vast majority of clinical practice in LMICs is based on the evidence from high-income countries, and that this should not be any different for therapeutic hypothermia, particularly considering the lack of any alternative.

Further concerns focus on the likely substantial cost of an adequately powered cooling trial with appropriate follow-up. In particular, the heterogeneity of the populations, infrastructures, and health systems all affect the follow-up rate in developing countries, especially in remote areas. In addition to this, multinational collaborations will be essential to provide the necessary support.

Despite the lack of evidence on safety and efficacy, many neonatal units in LMICs are now offering cooling therapy. (19)(20) Thus, some now argue that it is no longer ethical to randomize infants to usual care. We recently conducted a survey of 90 tertiary Indian neonatal units. Forty-seven (52%) offered therapeutic hypothermia; however, in the vast majority of cases, cooling practices were outside the protocols established in high-income countries. (8)

FIRST DO NO HARM

In several instances, direct extrapolation of the evidence from high-income countries to LMICs has resulted in harm. Two particularly high-profile trials are the Fluid Expansion as Supportive Therapy (FEAST) trial and the Antenatal Corticosteroids Trial (ACT). (21)(22) The FEAST trial examined fluid bolus for septic shock in African children and was discontinued because of an increased mortality rate in the intervention arm. (22) The ACT trial, a large cluster randomized trial in LMIC, showed that antenatal corticosteroids given to pregnant women in preterm labor (standard clinical practice in high-income countries) was associated with an increase of 12% in overall newborn mortality. (21) Without this trial, the worldwide usage of antenatal corticosteroids could have unintentionally caused the deaths of thousands of infants. (23)

The Hypothermia for Encephalopathy in Low- and middle-Income countries (HELIX) feasibility study examined the feasibility and effectiveness of a low-cost whole-body servo-controlled cooling device (Fig 2) in 5 large public neonatal units in India and highlighted significant population differences in infants with encephalopathy in LMICs. (24) In particular, meconium-stained amniotic fluid was found in 19 infants with NE (27%). The mean birthweight was 2,901 g, which is much lower than that reported in high-income countries. (25)(26) These results also showed a high incidence of gastric bleeding (25/49, 51%) in infants with NE who received cooling therapy, a finding that has not been shown in any previous cooling study in LMICs.

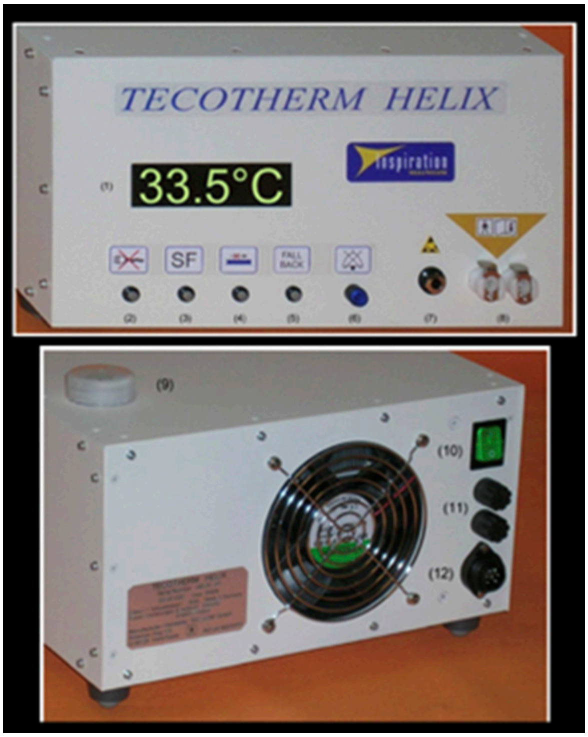

Figure 2. Whole body cooling using a low-cost servo-controlled prototype cooling device used in the Hypothermia for Encephalopathy in Low- and middle-Income countries (HELIX) feasibility trial.

THE NEED FOR MAGNETIC RESONANCE BIOMARKERS AND DISEASE STRATIFICATION

NE is rarely the result of a well-defined intrapartum event and several additional comorbidities come into play. Thus, it is not surprising that adverse outcomes are seen in up to 50% of the cooled newborns with encephalopathy in high-income countries. (2) In LMICs, where there are far more comorbidities, the efficacy of therapeutic hypothermia is even less certain. This represents a major roadblock to the clinical translation of therapeutic hypothermia in LMICs. However, a potential way forward is to develop "precision medicine" for NE using a 2-pronged approach: 1) applying magnetic resonance (MR) biomarkers to measure the effect of neuroprotective therapies and to understand the underlying etiology, and 2) profiling the host gene expression to allow disease stratification.

MR BIOMARKERS

MR biomarkers have the potential to overcome many of the challenging impediments to progress described herein, and have rapidly enhanced our ability to identify the condition, time the onset, and quantify features of brain injury soon after birth as well as the brain's longer-term responses to these insults. (27) There is now sufficient evidence to show that MR biomarkers can accurately predict long-term outcomes and serve as surrogate endpoints in clinical trials.

In particular, our group has shown that the measure with most prognostic value is based on MR spectroscopy of the deep grey matter nuclei, (28) which clearly identifies infants who are more likely to suffer long-term neurologic deficits. Moreover, the advantage of using quantitative MR biomarkers is that they have less variability than clinical neurodevelopmental outcome measurements, thus reducing sample size requirements. In addition, it is possible to avoid long delays between the neuroprotective intervention and outcome assessment.

Recent MR imaging findings in infants with NE in low-resource settings have shown a high prevalence of white matter injury on conventional MR imaging. More importantly, the brain injury seen in these settings is of perinatal origin, and hence potentially responsive to therapeutic hypothermia. Therefore, the use of MR biomarkers in LMICs seems essential to understand the nature of brain injury, and may be useful in developing neuroprotective strategies for this population. (29)

Although MR scanning is unrealistic in some low-income countries of sub-Saharan Africa, most middle-income countries, particularly in the Indian subcontinent, do have facilities for high-quality data acquisition. A recent survey of Indian neonatal units suggested that almost 80% of the units are offering MR imaging to infants with NE. MR imaging and spectroscopy may provide vital information about the nature, origins, and outcome of brain injury in this population, guiding the development of neuroprotective interventions.

A collaborative approach is certainly the only way forward. Although no single center has a sufficient number of infants with NE to set up an adequately powered trial, a consortium of different centers is essential for neuroprotection trials in which MR biomarkers can be used as a surrogate outcome measure. Moreover, this will increase the generalizability of the research findings, speed up dissemination, and rapidly translate putative neuroprotectants into clinical use.

THE CLINICAL HETEROGENEITY OF NE

Developing a targeted neuroprotection approach requires robust point-of-care tests for disease stratification, based on etiology and therapeutic pathways. Such a rapid, robust, and inexpensive test could guide treatment and correctly predict those children who will benefit the most from therapeutic hypothermia, and thus would have significant potential to change practice and improve outcomes. This is especially the case in LMICs, which bear the highest disease burden.

Gene expression profiling provides a snapshot of the biological processes that occur in response to internal or external stimuli. Changes in gene activity (expression) occur rapidly, and patterns of increased or decreased transcript abundance can provide both a route map of cellular pathologic processes, and a "signature" used for diagnostic or prognostic classification. Gene expression profiling is well established in cancer research for predicting clinical outcome, identifying the presence of metastases, and developing personalized treatment. (30)

More recently, minimal host gene expression signatures have been developed for disease stratification in both tuberculosis and bacterial infection, with a particular focus on LMIC. (31)(32) Point-of-care tests based on the minimal transcript for rapid diagnosis of bacterial infections are in development and will reach the clinics in the near future.

We recently reported a unique gene expression profiling in infants with NE, (33) which is consistent with the preclinical data (animal models) suggesting upregulation of genes involved in neurogenesis and autophagy. (34) Furthermore, an overall decrease of endocytic capacity has been found during hypoxia, suggesting an oxygen-dependent uptake of different macromolecular ligands, or a hypoxia-induced paralysis. (35)

At the moment, the biggest challenge is to use high-tech point-of-care personalized medicine in settings in which basic neonatal care is not provided. In fact, many researchers argue that it is unlikely that a neuroprotection-targeted approach will be useful in LMICs in the short to medium term, and that more resources should be focused on improving antenatal care instead. However, deriving the signature requires sophisticated technology and expertise, and the future implementation of a diagnostic gene expression signature will capitalize on the rapidly emerging global technology boom in low-cost bedside diagnostics. In particular, new technologies, such as quantum dots and nanopores, which make it possible to perform rapid high-throughput sequencing, are now emerging in the genomic field. (36)

THE WAY FORWARD

A large, randomized, controlled trial of hypothermia is currently ongoing across India, Bangladesh, and Sri Lanka. A total of 408 infants with moderate and severe encephalopathy will be randomized to either whole-body cooling using a servo-controlled cooling device or usual care. (37)

The HELIX trial is being conducted in parallel with the development of a simplified, automated, low-cost servo-control cooling device so as to tackle the significant staffing shortages experienced by most neonatal units in government-funded hospitals in LMICs.

As part of the trial, blood samples of all enrolled infants will be collected for gene expression, 3-Tesla MR imaging and spectroscopy will be performed, and a detailed neurodevelopmental assessment will be performed at 18 months. This is the first example in LMICs of such a large network, which relies on the use of novel biomarkers, and represents a unique opportunity for providing a definitive answer to questions about the efficacy of therapeutic hypothermia. Together, these centers offer a unique platform for neuroprotection trials and for developing new accurate biomarkers of adverse neurologic outcomes in infants with NE.

Although many adjunct neuroprotective therapies have proven efficacy in preclinical models of "pure hypoxic-ischemic injury," clinical translation is challenging because of NE heterogeneity. Only one-third of cases can be attributed to an acute intrapartum hypoxic insult, whereas subacute injury from perinatal infection and inflammation may be responsible for the vast majority of cases, especially in LMICs. Animal evidence suggests that hypothermic neuroprotection is lost in the case of coexistent infection, particularly with gram-negative organisms (38)(39); however, the clinical implications of these observations is unclear. Although neither MR spectroscopy nor gene expression are required as a part of routine clinical practice, their use at this stage will provide valuable information about disease mechanisms, and can guide the development and evaluation of neuroprotective therapies in NE. Without this, therapeutic failure at this stage would not only result in substantial waste and impediments to scientific progress, but may also expose more infants to possible side effects.

Once completed, the HELIX trial will provide the most comprehensive data about the efficacy of therapeutic hypothermia in LMICs, and can reveal the underlying pathologic mechanisms of NE in low-resource settings. This novel approach to an old problem has the potential of leading a paradigm shift in global perinatal health, transforming the way neonatal neuroprotectants are evaluated.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical features, diagnosis, and management of perinatal hypoxic ischemic encephalopathy.
- Know the causes, clinical features, evaluation, and management of hypoxic ischemic encephalopathy.

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Congenital Hypopituitarism in Neonates

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Education Gap

Early identification of congenital hypopituitarism is of utmost importance, because undiagnosed pituitary hormone deficits can lead to significant morbidity and possible mortality. However, the diagnosis can be challenging, because the clinical manifestations are often nonspecific. Clinicians should be able to recognize the signs and symptoms of congenital hypopituitarism and understand the appropriate diagnostic tests and treatment modalities.

Abstract

Patients with congenital hypopituitarism are born without normal production of 1 or more of the hormones normally produced in the pituitary gland. The clinical spectrum varies widely; although a number of genetic causes are known, most cases are thought to be idiopathic. Mutations in transcription factors involved in various stages of pituitary development can lead to combined pituitary hormone deficiencies. Many clinical signs and symptoms of congenital hypopituitarism are nonspecific and include poor weight gain, hypoglycemia, jaundice, and cholestasis; examination findings include midline defects. Diagnosis should include cranial imaging with magnetic resonance imaging, as well as laboratory evaluation for pituitary hormone deficits. Hormone replacement should be initiated after the diagnoses of deficiencies are confirmed.

Objectives

After completing this article, readers should be able to:

1. Describe the physiology of pituitary development and how genetic defects can result in hypopituitarism.
2. Recognize presenting clinical signs and symptoms of neonates with congenital hypopituitarism.
3. Review methods to diagnose and treat neonates with congenital hypopituitarism.

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ABBREVIATIONS

ACTH	adrenocorticotropin hormone
CPHD	combined pituitary hormone deficiencies
FSH	follicle-stimulating hormone
GH	growth hormone
IGF	insulinlike growth factor
IGHD	isolated GH deficiency
LH	luteinizing hormone
ONHS	optic nerve hypoplasia syndrome
T_3	triiodothyronine
T_4	thyroxine
TBG	thyroxine-binding globulin
THOP	transient hypothyroxinemia of prematurity
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone

INTRODUCTION

The pituitary gland lies in the center of the cranial base and helps regulate vital processes such as growth, metabolism, stress response, pubertal development, and lactation. It is formed from 2 different embryological sources that give rise to 2 sections, the anterior pituitary and the posterior pituitary. (1) The 6 hormones produced and secreted by the anterior pituitary are growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. The posterior pituitary hormone secretes antidiuretic hormone (also known as *vasopressin*) and oxytocin, which are produced in the hypothalamus.

Patients with congenital hypopituitarism can have a single isolated pituitary hormone deficiency or multiple pituitary hormone deficiencies, and may present early in the neonatal period or later in childhood. The clinical spectrum of severity varies widely, and may be associated with central nervous system malformations. (2) Although some cases are known to have genetic causes, in most cases, the causes have not been determined.

Early identification of congenital hypopituitarism is of utmost importance, because undiagnosed pituitary hormone deficits can lead to significant morbidity and possible mortality. However, the diagnosis can be challenging, because the clinical manifestations are often nonspecific and can mimic other disease processes; in addition, other etiologic factors can be responsible for the laboratory findings of hypopituitarism. This review highlights the normal development of the pituitary and transcription factors necessary for proper embryogenesis, the clinical presentation of hypopituitarism in neonates, methods for diagnosis, and management.

PITUITARY DEVELOPMENT AND COMBINED PITUITARY HORMONE DEFICIENCIES

The anterior pituitary is derived from the oral ectoderm of the Rathke pouch. Further cell determination and specification rely on the expression and interaction of multiple signaling molecules and transcription factors. (3) The first cells to differentiate are corticotrophs, followed by the gonadotrophs, and then the thyrotrophs and somatotrophs/lactotrophs. Transcription factors involved in these early stages of pituitary development include early developmental factors such as *HESX1*, *LHX3*, *LHX4*, *SOX3*, *GLI2*, and *OTX2* (Fig 1). Mutations in the genes for these factors have broad effects on fetal development and are each associated with specific syndromic features, with or without additional structural abnormalities. Although the frequency of known genetic defects in patients with combined pituitary hormone deficiencies (CPHD) is small (~16% of cases can currently be explained by mutations in known genes), clinicians should recognize developmental abnormalities that may be associated with hypopituitarism (Table 1). (4)

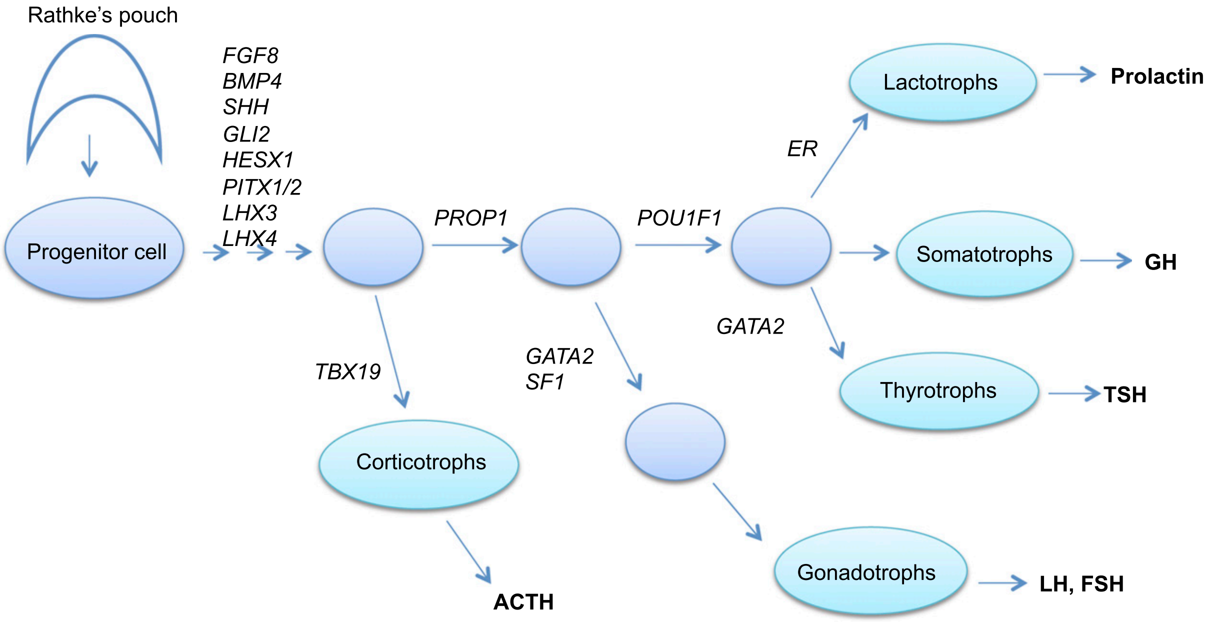

Figure 1. Simplified representation of anterior pituitary-specific cell type development and timing of expression of transcription factors. ACTH=adrenocorticotropin hormone; BMP4=bone morphogenic protein 4; FGF8=fibroblast growth factor 8; ER=estrogen receptor; FSH=follicle-stimulating hormone; GH=growth hormone; LH=luteinizing hormone; SF1=steroidogenic factor 1; SHH=sonic hedgehog; TSH=thyroid-stimulating hormone.

TABLE 1. **Early Developmental Factors and Clinical Presentation of Gene Mutations**

DEVELOPMENTAL FACTOR	CLINICAL PRESENTATION	POSSIBLE PITUITARY HORMONE DEFICITS
SOX2	Bilateral anophthalmia or severe microphthalmia, esophageal atresia, genital abnormalities, dental anomalies	FSH, LH deficiency; variable GH deficiency
SOX3	Craniofacial abnormalities with or without intellectual disability, hearing impairment, X-linked inheritance	Range from isolated GH deficiency to CPHD
OTX2	Micro-/anophthalmia, seizures	Range from isolated GH deficiency to CPHD
HESX1	Optic nerve hypoplasia syndrome and variants, ectopic posterior pituitary	Range from isolated GH deficiency to CPHD
LHX3	Spine abnormalities (short rigid cervical spine with limited neck rotation and trunk movement), variable degrees of sensorineural hearing loss	GH, TSH, FSH, LH, prolactin deficiency; variable ACTH deficiency
LHX4	Cerebellar abnormalities and Chiari malformation	GH, TSH, ACTH deficiency; variable FSH, LH deficiency
GLI2	Holoprosencephaly, cleft lip/palate, anophthalmia, postaxial polydactyly, single nares, central incisor	Range from isolated GH deficiency to CPHD

ACTH=adrenocorticotropin hormone; CPHD=combined pituitary hormone deficiencies; FSH=follicle-stimulating hormone; GH=growth hormone; LH=lutenizing hormone; TSH=thyroid-stimulating hormone

The spectrum of clinical phenotypes seen in patients with CPHD reflects the similar regulation seen during embryologic development of various organs (ie, eye/optic nerve, ear, nose, pituitary, some cranial nerve ganglia). Optic nerve hypoplasia syndrome (ONHS, formerly *septo-optic dysplasia*) is defined by the presence of at least 2 of the following: 1) optic nerve hypoplasia (small optic disc); 2) midline forebrain defects (underdevelopment of the septum pellucidum and agenesis of the corpus callosum); and 3) pituitary hypoplasia with variable hypopituitarism. (5)(6) Although many genes have been implicated (including *HESX1*, *SOX2*, *SOX3*), most cases are sporadic, without an identifiable mutation, likely multifactorial because of both genetic and environmental influences. Among patients with ONHS, 70% to 75% have some degree of hypopituitarism; endocrine abnormalities range from isolated GH deficiency (most commonly seen) to panhypopituitarism. (5) Recent data suggest that brain malformations in children with ONHS do not correlate with hypopituitarism and therefore are an unreliable screen for risk of CPHD. (7)

Holoprosencephaly, characterized by structural midline forebrain abnormalities resulting from abnormal hemisphere bifurcation, is the most common developmental disorder of the human forebrain. (8) The etiology is likely multifactorial, but includes mutations in fibroblast growth factor 8 (*FGF8*) and *GLI2*. The clinical spectrum is wide, with central diabetes insipidus the most common endocrine disorder; however, anterior pituitary dysfunction (ranging from isolated to CPHD) can still be seen. (9)(10) Patients with pituitary stalk interruption syndrome, a rare congenital defect, have a thin or absent pituitary stalk, ectopic posterior pituitary, and hypoplasia or aplasia of the anterior pituitary. Pituitary stalk interruption syndrome is associated with varying degrees of pituitary hormone deficiency. GH deficiency presents most frequently with or without additional hormone deficits. (11) An empty sella, if seen on imaging, has also been associated with pituitary hypofunction. (12)

In contrast, the pituitary-specific transcription factors *PROP1* and *POU1F1* (previously known as *PIT1*) are expressed later in anterior pituitary differentiation, and mutations in their genes result in variable phenotypes of CPHD without other syndromic features. (10) *PROP1* is necessary for the differentiation of cells that are a precursor to somatotrophs, lactotrophs, thyrotrophs, and gonadotrophs; *PROP1* mutations appear to be the most common cause of both familial and sporadic congenital CPHD; *POU1F1* acts immediately downstream of *PROP1* and allows for differentiation of cells that are a precursor to somatotrophs, lactotrophs, and thyrotrophs. (1)(4)

ISOLATED HORMONE DEFICIENCIES

Patients with congenital hypopituitarism can also display isolated hormone deficiencies. The most common, congenital isolated GH deficiency (IGHD), has a reported incidence ranging from 1 in 4,000 to 1 in 10,000. (13) Four genetic forms have been described. *GH1* gene abnormalities inherited in an autosomal recessive manner are the cause of IGHD type 1A (complete absence of GH) and type 1B (milder phenotype), and lead to decreased synthesis/secretion of GH. Type 2, the most common genetic form of IGHD, is inherited in an autosomal dominant fashion. Type 3 is a partial GH deficiency, inherited in an X-linked manner, and can be associated with hypogammaglobulinemia. (1)

Congenital isolated ACTH deficiency, characterized by low plasma ACTH levels resulting in low cortisol production, is rare. Although mutations in *POMC* and proconvertase 1 are known to cause ACTH deficiency associated with a wide range of phenotypes, *TBX19* (formerly *TPIT*) mutations have been shown to cause congenital isolated ACTH deficiency. First discovered in 2001 and further described in 2011, these mutations are responsible for two-thirds of neonatal-onset complete isolated ACTH deficiency. (14)(15)

Specific defects in thyrotropin-releasing hormone (TRH) or TSH signaling can lead to isolated central congenital hypothyroidism. The most common identifiable genetic cause of isolated central congenital hypothyroidism is immunoglobulin superfamily member 1 (*IGSF1*) gene deficiency. (16) *IGSF1* deficiency was first reported in a 2012 study of 11 families with X-linked central hypothyroidism and adult macro-orchidism, and since then, numerous cases have been described. (17) Rarer etiologies include defects in genes controlling TSH production, that is, mutations in the TRH receptor or TSH-B subunit. (18)(19)

CLINICAL PRESENTATION

Prior to delivery, clinicians should obtain a detailed medical history, because a family history of panhypopituitarism suggests increased risk. Disorders can be inherited in an autosomal dominant fashion (ie, presenting patient has an affected parent), an autosomal recessive manner (consider if the patient has an affected sibling with normal parents), or in an X-linked pattern (expect to see affected male maternal family members). In addition, a low maternal estriol plasma level during pregnancy has been reported to be a predictor of isolated ACTH deficiency. (20) Several studies suggest that children later diagnosed with hormone deficits have an increased incidence of breech delivery or cesarean section, prolonged or precipitous deliveries, intrapartum distress, or low Apgar scores. However, it is not well understood if the pituitary abnormality predisposes the neonate to other adverse events, or vice versa. (21)(22)(23)

Physical examination findings that may be associated with hypopituitarism include midline abnormalities, such as midface hypoplasia and cleft lip or palate (Table 2). In addition, boys with congenital hypopituitarism can present with micropenis secondary to GH deficiency and/or gonadotropin deficiency. (24) Because fetal growth is independent of GH but rather, influenced by maternal nutrition and placental function and mediated via insulin and insulinlike growth factors (IGF) I and II, neonates with GH deficiency often have a normal size at birth. (25)

Although neonatal hypoglycemia is a nonspecific symptom, it is a common finding in the setting of GH deficiency and/or adrenal insufficiency. GH and cortisol are important counter-regulatory hormones and act to increase gluconeogenesis in fasting states. Shortly after birth, most neonates are able to maintain a plasma glucose concentration between 55 mg/dL (3.05 mmol/L) and 65 mg/dL (3.6 mmol/L), which should subsequently increase to more than 70 mg/dL (3.9 mmol/L) by 2 to 3 days after birth. (26) Infants noted to have refractory hypoglycemia with ketosis should raise concern for possible hypopituitarism. Symptoms of hypoglycemia are somewhat nonspecific and include jitteriness, cyanosis, seizures, apneic episodes, tachypnea, lethargy, or poor feeding. (27) Patients with multiple pituitary hormone deficits have been found to have a greater incidence of hypoglycemia than those with isolated GH deficiency. (25) Additional clinical clues include failure to thrive (ie, weight loss or poor weight gain); in extreme scenarios, central adrenal insufficiency can lead to adrenal crisis.

In addition, it has been shown that certain hormone deficiencies (hypothyroidism, adrenal insufficiency, or GH deficiency) can alter liver function; while the pathologic method is unclear, infants with CPHD have been known to present with prolonged hyperbilirubinemia. (28) Although infants with hypothyroidism present with indirect hyperbilirubinemia, infants with GH and ACTH deficiency

TABLE 2. **Clinical Manifestations of Congenital Hypopituitarism**

	CLINICAL MANIFESTATIONS OF CONGENITAL HYPOPITUITARISM
Physical examination	Midline defects (cleft palate, midface hypoplasia) Micropenis Failure to thrive, poor weight gain or weight loss Hypothermia
Laboratory or imaging	Hypoglycemia Hyperbilirubinemia/cholestasis Magnetic resonance imaging abnormalities

present with direct hyperbilirubinemia, and cholestatic jaundice has been found in as many as 35% of neonates with congenital hypopituitarism. (29) It is important to note that the pattern of liver dysfunction in these patients is variable, ranging from mild indirect hyperbilirubinemia to cholestasis, hepatomegaly, and elevated transaminase or γ-glutamyltransferase levels, and can be confused with biliary atresia. (28)(30)

Diabetes insipidus is characterized by excessive excretion of large volumes of dilute urine. The most apparent signs in infants may be crying/irritability, poor growth and/or weight loss, or hyperthermia as a result of dehydration and hypernatremia if fluid intake does not keep up with urine output. If patients have concurrent central adrenal insufficiency, the classic symptoms may be masked because glucocorticoid deficiency can lead to increased reabsorption of water. (31)

DIAGNOSIS

The differential diagnosis for acute hypoglycemia, failure to thrive, and cholestasis includes sepsis. Therefore, clinicians should be aware of the concurrent possibility of an endocrinologic disorder, especially if any of the aforementioned physical examination findings are noted. Brain magnetic resonance imaging with contrast administration is the preferred modality for assessing the pituitary; optimal information is obtained with high-resolution images with thin cuts (2-3 mm thick) through the pituitary. In newborns, the pituitary gland is usually convex, sometimes pear-shaped, with high signal intensity on T1-weighted images (Fig 2A). (32) Patients with multiple pituitary hormone deficiencies tend to exhibit abnormalities on imaging (ranging from a hypoplastic pituitary gland without other anatomic abnormalities to a severely hypoplastic pituitary gland with ectopic posterior pituitary and an interrupted or hypoplastic pituitary stalk); however, normal imaging does not always correlate with severity of pituitary hormone deficits (Fig 2B). In addition, some abnormalities, such as a small pituitary or an ectopic posterior pituitary with a normal pituitary stalk, may not be associated with pituitary hormone deficiencies. (33) A “bright spot” identifies the posterior pituitary gland, but this may be absent in 10% of normal individuals. (32)

Hormone deficiencies can be identified with laboratory testing. Central hypothyroidism is characterized by a low free thyroxine (T_4) level with low or inappropriately normal TSH level. Although central congenital hypothyroidism may be detected on primary T_4-based newborn state screening if the total T_4 level is frankly low, it is missed on TSH-based screening strategies used by most newborn screening programs worldwide. (34)(35) Some experts have suggested that a screening strategy based on T_4 may actually be more cost-effective than TSH-based screening. (16)(36) Clinicians should be aware of the screening process in their state/region, because these processes vary across the country and around the world. A confounding factor in screening for central hypothyroidism is that the pattern of normal TSH with low T_4 can also be seen in thyroxine-binding globulin (TBG) deficiency, in hospitalized patients (termed *nonthyroidal illness*), and furthermore, in premature infants, termed *transient hypothyroxinemia of prematurity* (THOP). Complete X-linked TBG deficiency occurs in approximately 1 in 15,000 boys and is characterized by low total T_4 with normal TSH; although typically free T_4 levels are normal, some assays may give falsely low levels in the setting of assay-binding difficulties, in which case total T_4 and TBG index (ie, triiodothyronine [T_3] uptake) can be measured, and the diagnosis can be confirmed with measurement of TBG. (37) Nonthyroidal illness causes a suppression of hypothalamic TRH synthesis, leading to low plasma T_4 and T_3 levels in the setting of normal or slightly decreased TSH concentrations; it is generally considered a protective mechanism against thyroid-hormone-mediated metabolic stimulation. (38) THOP is a self-limiting alteration in thyroid hormone availability seen in premature infants born before 30 to 32 weeks (and half of infants born before 28 weeks); reduced T_4 levels seen postnatally in these infants are reflective of relative immaturity of the hypothalamic-pituitary-thyroid axis and thought to be from a decreased magnitude of the postdelivery TSH and T_4 surge, in addition to the loss of maternal and placental transfer of T_4, decreased thyroidal iodine stores, decreased TBG levels, and increased sensitivity to thyroid-suppressive effects of iodine exposure. (39)(40)(41) In addition, various medications used routinely in this population can cause abnormalities in thyroid function testing without overt thyroid dysfunction, including pressors (dopamine/dobutamine), glucocorticoids, and diuretics. Although the differential diagnosis for abnormal thyroid function testing is broad, the constellation of signs and symptoms described herein, in conjunction with abnormal newborn screening and/or laboratory abnormalities, should alert providers to the possibility of congenital hypopituitarism.

Evaluating for GH deficiency in a neonate is different than that in an older child. Random serum GH levels are high during the neonatal period, which allows for the diagnosis of GH deficiency to be made without provocative testing; while secretory peaks are higher in the term neonate in the first 5 to 7 days after birth than throughout childhood, they decline quite rapidly in subsequent weeks. (33)(42)

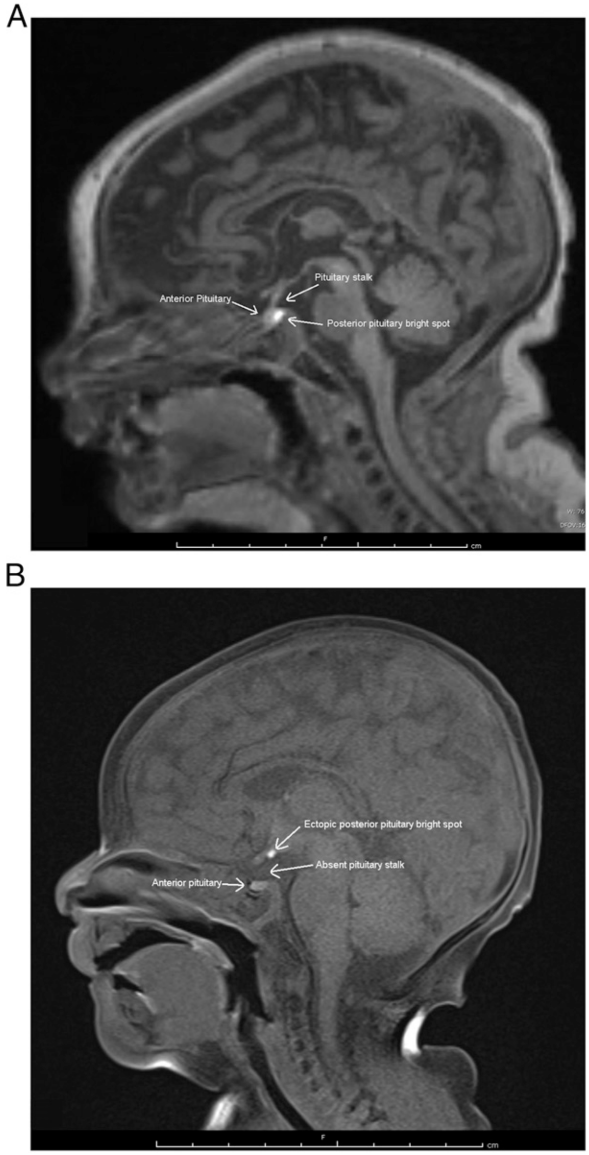

Figure 2. A. Magnetic resonance imaging (MRI) scan of a 9-day-old infant with a normal pituitary gland. B. MRI scan of a 7-day-old infant with ectopic posterior pituitary and absent infundibulum.

IGF-I, whose production is stimulated by GH, is used as a screening test for GH deficiency in older children. However, IGF-I levels remain low for at least the first 15 to 18 months of age and thus are difficult to interpret in this population. (21) A random GH level of less than or equal to 5 ng/mL (5 μg/L) in the first week after birth in association with other pituitary hormone deficiencies is sufficient to diagnose GH deficiency. (33)

In hospitalized neonates, assessment of the hypothalamic-pituitary-adrenal axis can be confounded by concurrent glucocorticoid use, because topical, enteral, parenteral, and inhaled corticosteroids can all lead to ACTH suppression. In addition, structurally related endogenous and exogenous hormones including hydrocortisone and prednisolone (conversion product of prednisone) can cross-react with steroid hormone immunoassays, and lead to falsely elevated results. (43) Although morning cortisol levels can be useful in evaluating ACTH deficiency in older individuals, neonates do not have a diurnal circadian rhythm (which is not established until at least 2 months of age) and therefore, the diagnosis cannot and should not be made in the setting of a low serum cortisol concentration. Many patients require a dynamic assessment, which can be completed via stimulation testing with cosyntropin, though this testing has lower sensitivity in patients with central adrenal insufficiency. (44) Stimulated cortisol values greater than or equal to 18 μg/dL (497 nmol/L) suggest an intact hypothalamic-pituitary-adrenal axis. (45) It remains controversial whether low-dose (1 μg) or high-dose (250 μg) cosyntropin should be used to diagnose central adrenal insufficiency, whether a lower dose of high-dose cosyntropin (ie, 62.5 μg or 15 μg/kg) should be used in neonates, what the timing for collecting cortisol samples after both low-dose and high-dose cosyntropin is, and if the cutoff peak cortisol level for low-dose cosyntropin should be lower than that for high dose. Of note, low cortisol or GH levels at the time of a hypoglycemic episode have low specificity for diagnosing GH deficiency or adrenal insufficiency, and thus a single low cortisol or GH value measured at the time of hypoglycemia should not be the only test for diagnosing these hormone deficits. (46)

Infants experience a surge in the gonadotropins LH and FSH and in sex steroids (ie, estradiol or testosterone), which is evident by 2 weeks after birth. In boys, this “minipuberty” lasts for several months after birth; in girls, it can last up to 2 to 3 years. This postnatal gonadotropin surge is a useful time to explore the integrity of the hypothalamic-pituitary-gonadal axis, because pubertal gonadotropin levels suggest an intact axis. (47) Lastly, prolactin secretion is normally regulated in a negative manner by dopamine from the hypothalamus. Although prolactin levels can be elevated in patients with cranial malformations leading to hypothalamic-pituitary stalk damage, prolactin levels are also elevated in neonates after birth (and can persist for at least 6 weeks after birth), making interpretation of levels difficult; a low prolactin in this population could suggest a problem with lactotroph development. (48)

Because neonates (especially those born prematurely) generally do not concentrate urine as efficiently as older children, diagnosing central diabetes insipidus in this population can be quite challenging. After confirming the presence of polyuria (>4 mL/kg per hour in an infant, >6 mL/kg per hour in a neonate), obtaining concurrent urine and serum osmolality measurements is recommended. Urine osmolality less than 300 mOsm/kg at the time of serum osmolality greater than 300 mOsm/kg is suggestive of the diagnosis. However, the use of agents that can cause osmotic diuresis, such as glucose/saline load, mannitol, or contrast agents, must be ruled out, as should neonatal diabetes mellitus; hypercalcemia and hypokalemia can also interfere with renal concentrating mechanisms. If urine osmolality can be concentrated to more than 600 mOsm/kg, diabetes insipidus can be effectively ruled out. Resolution with subcutaneous vasopressin distinguishes a central etiology from a nephrogenic one. Performing a water deprivation test in a neonate (in which fluids are withheld and serum sodium levels, urine output, and weight are measured over time) is not recommended. (31) In addition, vasopressin levels are difficult to measure because the molecule degrades quickly.

MANAGEMENT

If a neonate with hypopituitarism presents with hypoglycemia, treating early with dextrose-containing intravenous fluids is of utmost importance to prevent irreversible neurologic damage. Unlike hypoglycemia that results from hyperinsulinism, euglycemia can be maintained in patients with hypopuitarism-induced hypoglycemia with maintenance glucose infusion rate. Hormone replacement should only be initiated after diagnoses of deficiencies are confirmed.

Cortisol deficiency should be detected and treated before levothyroxine replacement to avoid an adrenal crisis. If central adrenal insufficiency is present, hydrocortisone doses should be initiated at 9 to 12 mg/m^2 per day divided 3 times daily. This dose is slightly higher than in older infants and children with central adrenal insufficiency, taking into consideration that neonates have increased cortisol secretion rates; dose titration is important, however, to prevent subsequent overtreatment, which can have a negative impact on growth and bone health. Concurrent mineralocorticoid treatment is not necessary, because children with central adrenal insufficiency have a normal renin-angiotensin-aldosterone axis, and thus, normal mineralocorticoid secretion. In periods of stress (eg, temperature >101°F [38.3°C], vomiting, surgery) patients should be started on stress dose steroids dosed as hydrocortisone 30 to 50 mg/m^2 per day divided every 6 to 8 hours, continued for 24 hours after the stressor has resolved. (45)

Central congenital hypothyroidism should be treated with levothyroxine tablets that are crushed and suspended in a few milliliters of formula, breastmilk, or water and administered orally; guidelines recommend an initial dose of 10 to 15 μg/kg per day. (49) Levothyroxine suspensions can potentially settle and lead to unreliable dosing. Although pharmacologic liquid formulations are now available, data on bioequivalence between drops and tablets are conflicting, suggesting the need for additional long-term studies before these formulations are considered reliable for treatment in this population. (50)(51) If oral administration is not possible, levothyroxine can be administered intravenously with a dose that is 75% of the oral dose. (52) The adequacy of T_4 replacement is best assessed by thyroid hormone measurements followed every 2 to 4 weeks while in the neonatal period, and levels should be maintained in the mid-upper half of the normal range. (34) Levothyroxine absorption can be affected by soy, iron, or calcium, and thus should not be coadministered with those vitamins/supplements or soy-based formula; in addition, anticonvulsants can lead to increased degradation, so levels should be followed closely in patients taking these medications. Although levothyroxine absorption is optimal on an empty stomach, fasting conditions can be difficult to achieve in a neonate; thus, the priority should be on consistent dose timing.

The starting doses of GH are 0.16 to 0.24 mg/kg per week (22-35 μg/kg per day); only preservative-free formulations are approved in neonates and should be administered subcutaneously in the evening on a daily basis. (33) IGF-I levels should be followed at least every 3 months. While cholestasis often resolves after initiation of hormone replacement in children with CPHD, interventions including ursodeoxycholic acid may need to be considered. (53) Boys who present with micropenis can be treated with testosterone enanthate or cypionate during infancy.

Central diabetes insipidus in neonates is often best treated with fluid repletion; full antidiuresis is not appropriate in these young patients, because the fluid restriction required does not allow for adequate caloric needs (ie, breast milk or formula). Neonates are ideally given a low-solute diet, with a thiazide diuretic potentially added to reduce urine output. Low-dose once-daily desmopressin can be considered (preferably administered subcutaneously); however, a period of breakthrough must be achieved to ensure appropriate caloric intake and reduce risk of hyponatremia from fluid overload. (31)

In addition to hormone replacement, patients with congenital hypopituitarism should have an ophthalmology evaluation for fundoscopic examination of the optic discs to assess for optic nerve hypoplasia. Evaluation may also include visual-evoked potentials and automated brainstem-evoked responses to evaluate for other coexisting developmental abnormalities. In certain scenarios, genetic screening/testing may be warranted. If a mutation is identified in a gene that results in an isolated pituitary hormone deficiency, providers and families can be reassured that additional hormone deficits will not develop. However, patients who present with mutations in transcription factors will require long-term surveillance for the development of other pituitary hormone deficiencies.

Continued follow-up of patients with congenital hypopituitarism is of utmost importance given the risk of developing additional deficiencies and evolving dysfunction. Thus, establishing care with a pediatric endocrinologist after discharge allows for continued screening and management.

CONCLUSION

Given the pituitary gland's major role in homeostasis and metabolism, neonates who present with congenital hypopituitarism are at risk for clinical decompensation if there is a delay in diagnosis. Unfortunately, identifying neonates with congenital hypopituitarism is not always straightforward, because many of the presenting symptoms are nonspecific. Clinicians should look for a constellation of findings to help with early diagnosis and treatment.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes of micropenis, including pituitary deficiency.
- Know the causes (including hyperinsulinemic hypoglycemia) of neonatal hypoglycemia syndromes.

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1. The pituitary gland is critical in the regulation of growth, metabolism, stress response, puberty, and lactation. The anterior and posterior sections of the pituitary gland arise from 2 distinct embryological sources. Which of the following hormones is produced by the posterior pituitary?

   A. Growth hormone (GH).
   B. Antidiuretic hormone.
   C. Prolactin.
   D. Thyroid-stimulating hormone (TSH).
   E. Adrenocorticotropic hormone (ACTH).

2. Congenital hypopituitarism may present as combined or isolated pituitary hormone deficiencies. Optic nerve hypoplasia syndrome (ONHS, formerly known as *septo-optic dysplasia*) is one of the more common types of congenital hypopituitarism and is diagnosed in patients with at least 2 of the 3 following findings: optic nerve hypoplasia, midline forebrain defect, and pituitary hypoplasia. The hypopituitarism in ONHS is variable. Which of the following endocrine abnormalities is most commonly found in patients with ONHS?

   A. Panhypopituitarism.
   B. Central diabetes insipidus.
   C. TSH deficiency.
   D. Isolated GH deficiency.
   E. ACTH deficiency.

3. The identification of neonates with congenital hypopituitarism is challenging because the clinical presentation is often nonspecific. Which of the following physical examination findings is NOT consistent with the diagnosis of congenital hypopituitarism?

   A. Small-for-gestational age birthweight.
   B. Cleft lip or palate.
   C. Micropenis.
   D. Midface hypoplasia.
   E. Persistent jaundice.

4. The diagnosis of congenital hypopituitarism requires laboratory findings that may be different in neonates compared with children or adults. Which of the following statements is correct about the diagnostic evaluation of hormone deficiencies in the newborn?

   A. Random serum GH levels are not helpful in the neonatal period and assessment of stimulated GH levels is required for the diagnosis of GH deficiency in this population.
   B. TSH-based screening strategies will detect central congenital hypothyroidism.
   C. Neonates do not have a diurnal circadian rhythm of cortisol secretion until 2 months of age.
   D. Measuring vasopressin levels is the only reliable way to confirm the diagnosis of diabetes insipidus in the neonatal period.
   E. The integrity of the hypothalamic-pituitary-gonadal axis cannot be assessed in the immediate postnatal period because of the postnatal gonadotropin surge.

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5. Hormone replacement is the mainstay of treatment for neonates with congenital hypopituitarism. Which of the following statements about hormone therapy for neonates with congenital hypopituitarism is FALSE?

   A. Cortisol deficiency should be detected and treated before levothyroxine replacement to avoid adrenal crisis.
   B. Anticonvulsant therapy decreases the degradation of levothyroxine, leading to a decrease in dosing requirements.
   C. Fluid repletion using a low-solute diet is the first-line treatment strategy in neonates with central diabetes insipidus.
   D. During GH therapy, insulinlike growth factor I levels should be followed at a maximum interval of every 3 months.
   E. Concurrent mineralocorticoid treatment is not necessary in neonates with central adrenal insufficiency because these neonates have a normal renin-angiotensin-aldosterone axis.

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Posterior Urethral Valves: Prenatal, Neonatal, and Long-Term Management

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Education Gaps

1. Posterior urethral valve disorder is a condition that can manifest in utero and may be life-threatening in the neonatal period.
2. Lifelong urologic and renal follow-up are important for managing bladder and renal deterioration in patients with posterior urethral valves.
3. The degree of renal dysplasia occurring in patients with posterior urethral valves is the primary outcome predictor.

Abstract

A posterior urethral valve (PUV) is a membranous fold within the lumen of the posterior urethra that causes functional obstruction of the urine outflow. It is a common cause of obstructive uropathy in boys during the neonatal period. The disorder varies in its severity; in extreme cases, PUVs can be incompatible with postnatal life while other patients can suffer from renal and respiratory failure associated with oligohydramnios. Milder cases can present later in life with urinary incontinence and other urinary symptoms. The management of patients with PUVs remains a clinical challenge and includes endoscopic surgical resection of the urethral valve and follow-up during early infancy and adulthood to avoid progressive bladder dysfunction and monitor for chronic renal disease. This review will address the management of PUVs during the prenatal period, the neonatal period, and throughout the entire life of the patient.

Objectives After completing this article, readers should be able to:

1. Describe the prenatal evaluation and intrauterine management of fetuses with posterior urethral valves.
2. Summarize the management strategy of neonates with posterior urethral valves.

AUTHOR DISCLOSURE Drs Fishberg, Landau, Duvdevani, Gofrit, Friedman, and Hidas have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

BUN	blood urea nitrogen
ESRD	end-stage renal disease
MRI	magnetic resonance imaging
PLUTO	Percutaneous vesicoamniotic shunting for Lower Urinary Tract Obstructions
PUV	posterior urethral valve
VCUG	voiding cystourethrography

3. Explain the embryology and pathophysiology that can result in bladder and renal failure in patients with posterior urethral valves.
4. Recognize the lifelong management of incontinence and decreased renal function in most patients with posterior urethral valves.

INTRODUCTION

Posterior urethral valves (PUVs) are among the most devastating anomalies that occur in the urinary tract and are among the few that are life-threatening during the neonatal period. The lesion usually results in lifelong disabilities including urinary incontinence and decreased renal function despite optimal medical management. (1)(2)

The exact embryologic mechanism that causes PUVs is not completely understood. (3) It is hypothesized that PUVs result from disruptions in the embryologic development of the male urethra between 9 and 14 weeks' gestation. The inheritance of PUVs is also poorly understood and may involve multiple genes and various inheritance patterns. (4)

The incidence of PUVs is reported as 1.6 to 2.1 per 10,000 live male births. (5)(6) This incidence has decreased over the years in specific populations in which prenatal diagnosis and subsequent termination of affected fetuses are performed. In one report, 46% of fetuses diagnosed with valves were electively terminated. (7)

PUVs are membranous folds that obstruct the lumen of the posterior urethra. The effects of this urethral obstruction can be seen on the entire urinary tract. Because the obstruction is initiated in early fetal development, it creates high pressure in both the urine storage and voiding phases, which in turn, causes bladder muscle hypertrophy and hyperplasia along with increased connective tissue deposition. This leads to decreased bladder compliance, further amplifying the high storage and voiding pressures. Without treatment, this condition can result in end-stage bladder disease, manifested as renal damage, urinary incontinence, vesicoureteral reflux, and recurrent urinary tract infections. Although bladder function improvement has often been detected after valve ablation, the renal and ureteral damage can be severe and irreversible despite relief of the distal obstruction.

Renal injury in patients with PUVs is heterogeneous and can range from mild to severe renal failure early in life. Renal damage is related to renal dysplasia, and stems from both increased pressure during fetal development of the kidney and abnormal embryologic development. Tubular damage can manifest as nephrogenic diabetes insipidus. Because renal dysplasia is irreversible, the degree of dysplasia determines the long-term renal function.

During pregnancy, a fetal diagnosis of severe PUVs may be associated with varying degrees of oligohydramnios, which can affect many aspects of development leading to musculoskeletal deformities such as clubfoot, deformed hands, poor abdominal muscle tone, and Potterlike facies. Pulmonary hypoplasia is the most severe complication of PUVs and the most common cause of perinatal mortality. (8)

PRENATAL DIAGNOSIS AND MANAGEMENT

Most patients with PUVs are diagnosed using prenatal ultrasonography. Intrauterine obstruction can lead to bilateral hydroureteronephrosis and a distended and thickened bladder (Fig 1). This combination of findings has a high sensitivity (95%) and specificity (80%). The findings of oligohydramnios and a dilated posterior urethra displaying the "keyhole sign" (Fig 2) further corroborate the presence of lower urinary tract obstruction. (9)(10) The finding of increased renal echogenicity is also associated with PUVs; approximately 87.5% of patients with PUVs have been found to have increased echogenicity at a mean gestational age of 26 weeks. (11)(12)(13) Oligohydramnios is also a common

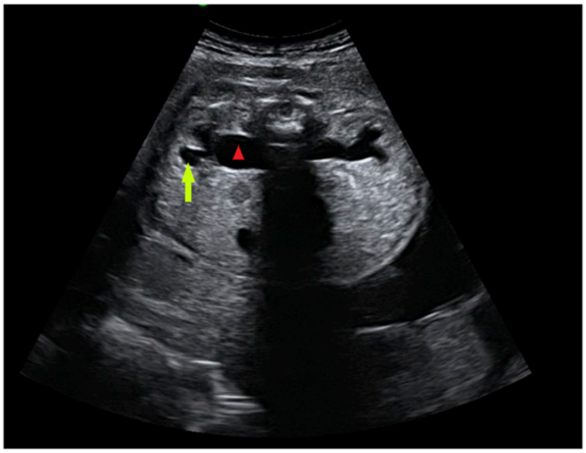

Figure 1. Prenatal ultrasonogram of a fetus at 27 weeks' gestation demonstrating dilated calyces (yellow arrow) and hydronephrosis (red triangle).

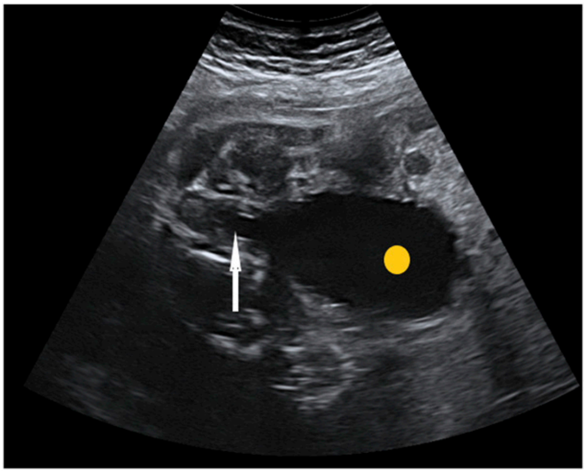

Figure 2. Prenatal ultrasonogram of a fetus at 32 weeks' gestation showing a thickened bladder (yellow circle) with a dilated posterior urethra (white arrow). This combination is consistent with the "keyhole sign."

fetal ultrasonographic finding in affected fetuses, as fetal urethral obstruction leads to decreased urine output. Any male fetus with bilateral hydroureter, oligohydramnios, and a distended bladder should be considered to have PUVs until proven otherwise, and prenatal consultations should include a discussion with families that an early postnatal ultrasonogram and voiding cystourethrography (VCUG) will likely be needed before the infant is discharged from the postpartum unit. (14)

Fetal magnetic resonance imaging (MRI) is rarely used to evaluate fetuses with PUVs. As with ultrasonography, fetal MRI can distinguish the degree of the ureteral obstruction. Further uses of the MRI are aimed at evaluating the degree of lung hypoplasia and cystic changes in the renal parenchyma. Although MRI provides additional analysis about the causes of obstruction in select cases, overall, the usefulness of MRI in diagnosing the actual cause of lower urinary tract obstruction, as with ultrasonography, is limited. (15)

The need to intervene during pregnancy to relieve the obstruction is controversial. Because dysplastic renal damage occurs in early gestation, mostly before the PUV is diagnosed, the improvement of renal function by antenatal interventions is minimal. The rationale for antenatal management of the associated severe hydronephrosis is to maximize normal development of the kidneys and to augment pulmonary function because severe oligohydramnios during the second trimester is usually associated with a high postnatal mortality as a result of pulmonary hypoplasia. The timing of onset of oligohydramnios has been shown to be an important determinant of the pulmonary and renal outcome. (16)(17) In the setting of less severe obstruction, when oligohydramnios can appear later in gestation, the usefulness of urinary tract decompression or early delivery for pulmonary reasons is limited. Prenatal intervention is considered in fetuses with a normal karyotype, salvageable renal function, and prenatal ultrasonography findings that suggest PUVs without renal cortical cystic lesions.

Specific fetal urine values after 20 weeks of gestation can assist with prognosis. Normal fetal urine levels include sodium concentration less than 100 mEq/L (100 mmol/L), chloride less than 90 mEq/L (90 mmol/L), osmolality less than 200 mOsm/kg (200 mmol/kg), and $\beta 2$-microglobulin less than 6 mg/L. (18) Serial evaluation of fetal urine osmolality and electrolyte concentrations can assist with determining severity of renal disease and optimal timing of an intrauterine procedure. In addition, close postprocedure monitoring can assist with effectiveness of procedure. (19)

The mainstay of prenatal intervention is percutaneous vesicoamniotic shunt placement. The rationale for this procedure is to attempt to restore amniotic fluid levels to normal by shunting fetal urine from the obstructed urinary bladder to the amniotic sac, which could prevent lung hypoplasia and minimize additional injury to the developing kidneys. The risks associated with this intervention include induction of preterm labor, perforation of fetal bowel and bladder, fetal loss, fetal and/or maternal hemorrhage, and infection.

To date, the reported long-term outcomes of antenatal intervention for severe obstructive uropathy (eg, PUVs, prune-belly syndrome, urethral atresia) are associated with a great range of variability. (20)(21) *P*ercutaneous vesicoamniotic shunting for *l*ower *u*rinary *t*ract *o*bstructions was compared with conservative management in the PLUTO trial. (22) The results were limited because of the poor recruitment rate and pregnancy terminations and only 12 live births in each group were studied. The overall survival was very poor in both groups, which was attributed to pulmonary hypoplasia, with only 2 infants surviving to 2 years of age with normal renal function. (22) A trend toward improved survival at 28 days was found in the shunt group. (22) The risk for pregnancy loss was greater in the shunt group because of procedure-related complications and early rupture of membranes. (22) In another study, 20 male fetuses that underwent vesicoamniotic shunting for isolated lower urinary tract obstruction in the setting of normal or borderline urinary sampling parameters were followed up for a mean of 5.83 years. (23) The results showed a 1-year survival rate of 91%. Health-related quality-of-life parameters were similar to those of unaffected, healthy children. (23)

On review of the current medical literature and guidelines, there is a lack of data about the ideal timing for delivery of fetuses with PUVs. The current consensus is to recommend early delivery in the presence of oligohydramnios diagnosed after 32 weeks' gestation to improve fetal renal function. (24)

POSTNATAL CLINICAL PRESENTATION, DIAGNOSIS, AND MANAGEMENT

The placenta and limited role of the fetal lungs provides a safe intrauterine environment that protects the fetus with PUVs from the consequences of renal dysfunction and pulmonary insufficiency. However, this protection ceases after birth. If the PUVs lead to severe prolonged oligohydramnios, neonates will have varying degrees of pulmonary hypoplasia, and may present with varying degrees of respiratory distress and cyanosis, often requiring respiratory support after birth. Neonates can present with a weak or intermittent urinary stream, which is consistent with a lower urinary tract obstruction. In this case, a 5- or 8-Fr feeding tube, or similar caliber urinary catheter, should be inserted into the urethra. In addition to respiratory distress, newborns with PUVs usually present with signs of severe systemic illness such as intrauterine growth restriction, lethargy, and poor feeding.

The infant's initial physical examination may demonstrate diffuse edema. Abdominal palpation may reveal poor muscle tone and the abdomen may be distended because of urinary ascites or distended bladder or secondary to hydronephrosis. (25) Increased intraluminal pressure within the kidney can cause urine to be extravasated from the kidney and lead to urinary ascites. The highly absorptive mesothelial surface that lines the peritoneum alters the properties of the urine, masking the identity of the urine and making the diagnosis of urinary ascites more difficult. (25) To confirm a diagnosis of urinary ascites, the ascitic fluid can be evaluated after the upper urinary tract is drained via nephrostomy tubes.

VCUG is the most important modality in the evaluation of a neonate with PUVs because it allows us to understand the anatomy and lower urinary tract gross functionality. PUVs may appear identical to many congenital urinary anomalies such as an anterior urethral obstruction or urethral stricture. (24) Images of the urethra during voiding are needed to confirm the diagnosis of PUVs. VCUG images of patients with PUVs demonstrate a thickened and trabeculated bladder with diverticuli and severe vesicoureteral reflux (Fig 3). (26)

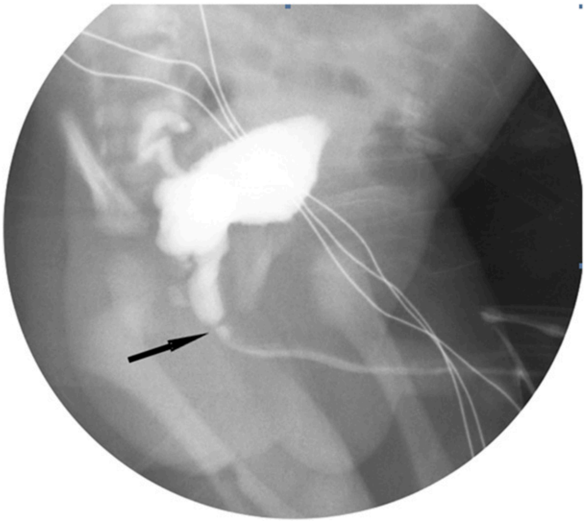

Figure 3. Voiding cystourethrogram of a 7-day-old neonate showing a bladder with multiple diverticuli and a dilated posterior urethra narrowing at the site of valvular obstruction (arrow indicates valve leaflet). Vesicoureteral reflux is seen on the left side of this voiding cystourethrogram.

Initial laboratory evaluation of the newborn with PUVs is usually misleading during the first few days after birth because of the residual effects of maternal renal function mediated through the placenta. The infant's initial creatinine and blood urea nitrogen (BUN) levels are usually similar to those of the mother, and it will take a few days for the serum levels to accurately represent the neonatal intrinsic renal function. Monitoring the infant's creatinine, BUN, and electrolytes twice a day in the first few days is recommended. Clinical monitoring including daily weight, urine output, blood pressure, and signs of infection is crucial.

If the diagnosis of PUVs has not been made prenatally, the most severely affected patients with PUVs present in the newborn period with a urinary tract infection or urosepsis. Although today PUVs are less commonly diagnosed after the neonatal period because of extensive prenatal ultrasonography, a recent study performed at Children's Hospital of Philadelphia showed that 43% of patients with PUVs presented after 6 months of age. (27) Most older children with a new diagnosis of PUVs presented with urinary tract infections, voiding complaints, and acute renal failure. (28) Therefore, a high degree of suspicion for PUVs is still warranted in boys with lower urinary tract symptoms, especially recurrent urinary tract infections, but also when overflow incontinence, gross hematuria, renal dysfunction, and less commonly, ejaculatory dysfunction are manifested. (29)(30)

After successful initial bladder drainage, the next medical step is to permanently resect the valves when the neonate is clinically stable. Endoscopic valve ablation is considered the preferred initial surgical option in a neonate diagnosed with PUVs. The treatment goal is to restore flow of urine through the urethra and enable normal cyclic filling and emptying of the bladder, which is superior to urinary diversion and passive urine drainage. (31)

After ablation, a urethral catheter is typically placed for at least 24 to 48 hours in an intensive care environment. Prolonged placement of a urinary catheter can help to monitor improvements in renal parameters. VCUG must be repeated after valve ablation within 1 to 3 months to ensure that the valves are no longer visible. Frequently, immediate signs of diminished bladder pressures, including some improvement in renal dilation and in the volume of vesicoureteral reflux, can be found.

With increasing practice of the miniature endoscopic technology, vesicostomy is reserved primarily for the very low-birthweight infant whose urethra cannot accommodate an 8-Fr endoscope, as well as a child with continued impaired renal function, high bladder urine volumes, and upper tract deterioration after valve ablation or urethral catheterization. Vesicostomy drainage serves as a bridging therapy to allow patients to preserve renal function and somatic growth until a definite treatment can be provided with incision of the valves. (32) The main disadvantage of vesicostomy is that the bladder stops cycling, which leads to detrusor atrophy and decreased bladder volume.

In cases of failed surgical interventions, upper urinary tract diversion enables direct decompression of the kidney by a cutaneous ureterostomy or pyelostomy that will produce direct, low-pressure urinary drainage, potentially optimizing renal function. Upper urinary tract diversion can be considered in an infant with complete decompression of the lower urinary tract but with worsening renal function, increasing upper tract dilation, and possibly a clinical presentation of sepsis. Internalization of the urinary tract after upper urinary tract diversion typically occurs between the ages of 3 and 5 years, allowing the upper tract and bladder enough time to rehabilitate. (33) In the case of expected renal failure, the reconstructive surgery should be delayed until renal transplantation. (33)

LONG-TERM OUTCOME OF PUVs

For patients with PUVs, management after successful surgical intervention includes detecting and treating bladder dysfunction, monitoring renal function, and, if necessary, managing the consequences of chronic kidney disease.

VCUG reveals vesicoureteral reflux in 50% to 80% of infants with the diagnosis of PUVs. (34) The associated reflux in patients with PUVs occurs as a result of bladder outlet obstruction, which increases pressures in the bladder; thus, relief of obstruction will decrease the pressures, resolve reflux in 25% to 40% of patients, and improve bladder trabeculation in most cases. (26)(34)

The severe hydroureteronephrosis, which is present in nearly all patients diagnosed with PUVs, usually resolves with relief of the obstructed bladder. (35) Hydronephrosis resolves in about half of all patients if they have no reflux, typically soon after valve ablation. (35) The remaining patients have persistent hydronephrosis despite proper drainage of the urinary system. (35)

Despite successful valve ablation, patients can still have long-term consequences. Intrinsic bladder dysfunction can lead to incontinence and upper tract deterioration. (36) Renal function can further worsen if drainage of the upper urinary tract is inadequate as a result of high storage pressure from the coexistence of high bladder volumes, poor bladder compliance, and decreased sensation. (36) Patients with PUVs are comfortable with high bladder volumes and elevated bladder pressures, which may lead to overflow incontinence and incomplete voiding. (37) This complication can be diagnosed based on abnormal urodynamics with decreased compliance and detrusor overactivity. (37) To decrease pressures and empty the bladder, affected patients can be initially treated by means of timed voiding. If this approach is ineffective, anticholinergic medications (eg, α-blockers) with endoscopic injection of botulinum toxin to the bladder can be used. (38) Clean intermittent catheterization and overnight bladder drainage is considered in patients with increased postvoid residuals, urinary tract infections, or worsening hydronephrosis and renal function.

Preservation of renal function and optimal renal growth and development are the primary management goals for patients with PUVs. As mentioned earlier, renal damage in affected patients is composed of 2 glomerular insults: dysplasia and obstructive uropathy. Because dysplasia decreases renal growth and development and is irreversible, it is the most important factor in determining long-term outcomes. (24) Lifelong urologic follow-up with monitoring of bladder function and assessment for infection is required in patients with PUVs to ensure that the patient's maximal renal potential is achieved. Overall, despite numerous advances in antenatal diagnosis and intervention, and rapid postnatal evaluation and treatment, the lifetime prevalence of end-stage renal disease (ESRD) in boys with PUVs is between 20% and 50%. (6)(39)

Ultrasonographic renal appearance is useful to assess the severity of dysplasia present in the kidneys. (40) Cystic changes in the cortex and loss of corticomedullary differentiation are linked with poor prognosis. (10) The severity of vesicoureteral reflux in patients with PUVs was found to be a prognostic factor for renal deterioration. (41)

Nadir creatinine at 1 month and 1 year of age has long been considered a relatively reliable method of predicting long-term renal outcome in affected children. (42)(43)(44) Serum creatinine of less than 0.8 mg/dL (70.7 μmol/L) appears to indicate a minimal risk, whereas a value greater than 1.2 mg/dL (106 μmol/L) at 1 year of age predicts a higher risk of developing ESRD. (42)(43)(44)(45)

The most common cause of ESRD in children is obstructive uropathy, accounting for 16.3% of children requiring renal transplantation. (46) Up to half of all patients with PUVs will require dialysis or renal transplantation as a result of ESRD likely during the first 2 decades of life. (24) The preferred management for children and adolescents with ESRD is renal transplantation as opposed to dialysis because of the advantages in quality of life and somatic growth seen after transplantation. Because the lower urinary tract is markedly abnormal in patients with PUVs, urologic complications such as urethral strictures, stone disease, and urinary retention are more common in this patient population. (47)

It must be emphasized that patients with PUVs have lifetime repercussions. Understanding these long-term risk factors and their impact on quality of life is necessary for counseling, preparing, and treating patients with PUVs as they reach adulthood. The lower urinary tract symptoms that affect children with PUVs also affect them as adults, 2 to 3 times more often than in the general population. (48) However, with modern management of renal insufficiency and bladder dysfunction, most patients with PUVs report a good quality of daily life. (49) The ability to father children has been found to be dependent on the presence or absence of uremia. (50)

CONCLUSION

PUVs are a heterogeneous birth defect with varying degrees of severity and correspondingly, different clinical manifestations. Some of these clinical outcomes can be devastating and life-threatening. Proper prenatal and neonatal management may alter the natural course of patients with PUVs. Lifelong monitoring is important to ensure renal function and maximize a patient's quality of life.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical manifestations of anatomic abnormalities of the kidneys and urinary tract in infants.
- Know how to diagnose specific anatomic abnormalities of the kidneys and urinary tract in infants.
- Know the recommended supportive and corrective treatment of anatomic abnormalities of the kidneys and urinary tract in infants.
- Know how prenatal diagnosis of renal abnormalities affects postnatal management.

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1. Posterior urethral valves (PUVs) are a common cause of obstructive uropathy in boys and represent the most common cause of end-stage renal disease in children. Which of the following statements is correct about PUVs?
    - A. While the precise embryologic mechanism of PUVs is unknown, a disruption in the development of the male urethra between 6 and 8 weeks' gestation is postulated to be the main cause of PUVs.
    - B. The incidence of PUVs has been increasing over the past decade.
    - C. Tubular damage does not occur in PUVs.
    - D. In addition to increased pressure in the entire urinary tract, abnormal renal embryologic development is an important contributor to renal dysplasia.
    - E. Severe renal dysplasia is the most common cause of perinatal mortality.
2. PUVs are most often diagnosed on prenatal ultrasonography. Which of the following ultrasound findings is NOT consistent with a prenatal diagnosis of PUVs?
    - A. Bilateral hydroureteronephrosis.
    - B. The presence of a "keyhole sign."
    - C. Decreased renal echogenicity.
    - D. Oligohydramnios.
    - E. The presence of a distended and thickened bladder.
3. Antenatal PUV intervention, most commonly percutaneous vesicoamniotic shunt placement, remains controversial. Which of the following statements is correct regarding prenatal interventions in fetuses with PUV?
    - A. The main benefit of shunting fetal urine from the obstructed bladder is to prevent renal dysplastic damage.
    - B. A fetal urine level of less than 100 mEq/L is a contraindication to the procedure.
    - C. Percutaneous vesicoamniotic shunting has been shown to improve health-related quality-of-life parameters.
    - D. In the percutaneous vesicoamniotic shunting for lower urinary tract obstructions (PLUTO) trial, patients in the shunt group had improved renal function at 1 year.
    - E. Studies of percutaneous vesicoamniotic shunt placement suggest a survival benefit in fetuses undergoing the procedure.
4. Postnatally, neonates with PUV require bladder drainage via a 5- or 8-Fr urinary catheter as well as close monitoring of their renal function. Which of the following statements regarding the postnatal course of neonates with PUV is INCORRECT?
    - A. Renal ultrasonography is the most important diagnostic modality for these patients.
    - B. PUVs may appear identical to other congenital urinary anomalies such as an anterior urethral obstruction or urethral stricture on voiding cystourethrography.
    - C. Endoscopic valve ablation is the preferred initial surgical option in neonates with PUVs.
    - D. Vesicostomy is the main surgical option for very low-birthweight infants.
    - E. Upper urinary tract diversion, either via cutaneous ureterostomy or pyelostomy, can be considered in patients with worsening renal function despite decompression of the lower urinary tract.

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5. Despite successful valve ablation in the newborn period, patients with PUVs face long-term challenges including bladder dysfunction, incontinence, chronic kidney disease, and a lifetime prevalence of end-stage renal disease between 20% and 50%. Which of the following is the most reliable predictor of poor long-term renal outcome in this population?

   A. Cystic changes in the cortex and associated loss of corticomedullary differentiation.
   B. A serum creatinine of 1.3 mg/dL (115 μmol/L) at 1 year of age.
   C. The presence of severe vesicourethral reflux.
   D. A history of need for respiratory support at birth.
   E. A history of recurrent urinary tract infections.

Posterior Urethral Valves: Prenatal, Neonatal, and Long-Term Management

Sharon E. Fishberg, Ezekiel H. Landau, Mordechai Duvdevani, Ofer N. Gofrit,
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1 The Impact of Methylergometrin Maleate Toxicity on Neonates

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AUTHOR DISCLOSURE Drs Badawy, Darwich, and Aqeel have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A full-term male neonate of 2.6 kg birthweight is born via a spontaneous vaginal delivery to a mother who denies any unfavorable obstetric or medical history. The delivery occurs at a peripheral hospital without any labor challenges. Approximately 20 minutes after delivery, the neonate develops central cyanosis and respiratory distress, for which he receives respiratory support in the form of oxygen through a nasal cannula. A decision is made to refer him to a tertiary NICU.

On arrival at the NICU, lung auscultation reveals bilateral equal air entry, no adventitious sounds, subcostal and intercostal recessions, a respiratory rate of 70 breaths/min, and oxygen saturation above 95% in room air. Normal first and second heart sounds are heard, plus a systolic 3/6 murmur over the left upper sternal border; the heart rate is 155 beats/min, mean blood pressure is 60 mm Hg (75/50 mm Hg), and echocardiography shows an insignificant patent ductus arteriosus and small atrial septal defect secundum.

The abdomen is soft and lax with no organomegaly detected. Neurologic examination shows lethargy, hypotonia, hyporeflexia of the deep tendon reflexes, and diminished primitive reflexes; the pupils are 2 mm in diameter with sluggish reaction to light bilaterally. Cranial ultrasonography depicts partially effaced ventricles as well as cerebrospinal fluid spaces denoting the possibility of brain edema (Fig 1); electroencephalographic monitoring is normal.

Electrocardiography (ECG) shows a sinus rhythm, normal rate, right axis deviation, initial QTc of 469 milliseconds, which increased to 532 milliseconds by the fourth day, then back to 500 milliseconds on the next day (it is interpreted as a significant prolonged QT interval) (Fig 2).

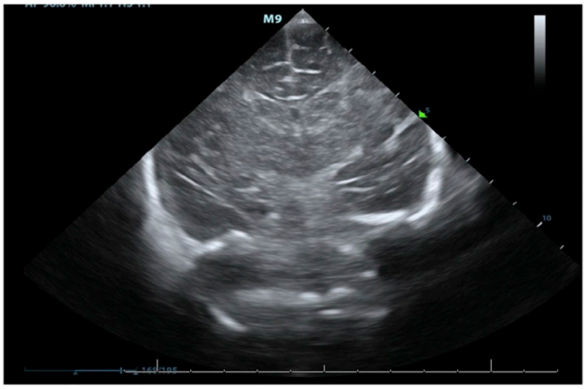

Figure 1. Cranial ultrasonographic scan showing a partially effaced ventricle as well as cerebrospinal fluid spaces that denote the possibility of brain edema.

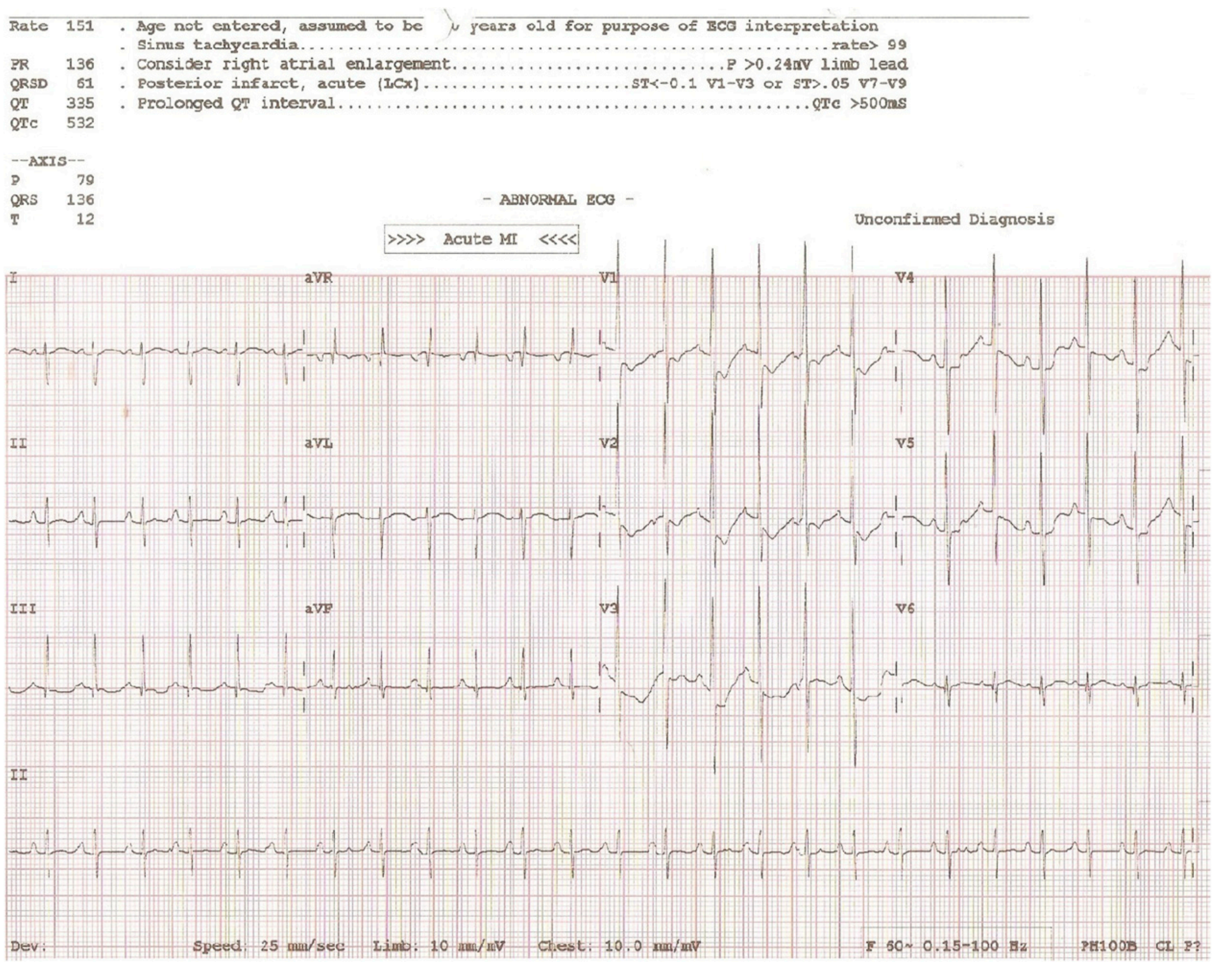
Rate 151 . Age not entered, assumed to be years old for purpose of ECG interpretation
. Sinus tachycardia....rate> 99
PR 136 . Consider right atrial enlargement....P >0.24mV limb lead
QRSD 61 . Posterior infarct, acute (LCx)....ST<-0.1 V1-V3 or ST>.05 V7-V9
QT 335 . Prolonged QT interval....QTc >500mS
QTc 532
--AXIS--
P 79
QRS 136
T 12
- ABNORMAL ECG -
Unconfirmed Diagnosis
>>>> Acute MI <<<<
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
Dev:
Speed: 25 mm/sec
Limb: 10 mm/mV
Chest: 10.0 mm/mV
F 60~ 0.15-100 Hz
PH100B
CL P?

Figure 2. Electrocardiography using 12 leads on the fourth day identifies sinus rhythm, normal rate, right axis deviation, and QTc of 532 milliseconds (which is interpreted as a significant prolonged QT interval).

Although laboratory findings are normal, the only abnormality identified is an elevated creatinine phosphokinase (CPK) level, which reaches 2,980 U/L then gradually declines to 249 U/L before discharge.

DISCUSSION

Differential Diagnosis

The list of differential diagnoses is long because the clinical picture is nonspecific; however, sepsis and birth asphyxia were considered on the top of the list.

Actual Diagnosis

Methylergometrin maleate intoxication as a medication error.

The Condition

Intramuscular vitamin K (phytomenadione) is usually prescribed to neonates as prophylaxis for hemorrhagic disease of the newborn. Although it is rare to misread the label of a vitamin K ampule, it occurs occasionally, as in the current case. The neonate was injected with 0.04 mg (0.015 mg/kg) intramuscular methylergometrin maleate, which was stored in the refrigerator instead of vitamin K, which commonly is stored on shelves outside. Even though this is difficult to discover, the assigned nurse honestly admitted her error.

Methylergometrin maleate (an ergot derivative) is used by obstetricians to reduce the possibility of postpartum hemorrhage through its action on the uterine smooth muscle and its vasculature.

Neonatal methylergometrin toxicity has a variable nonspecific presentation that could mimic other neonatal disorders, (1) therefore, it might be missed easily.

Morbidity and even mortality due to neonatal ergot poisoning are documented. (2)

Respiratory compromise is considered the most frequent presentation, ranging from distress and mild cyanosis, which needs minimal support, to apnea and respiratory failure, which needs ventilatory support. Some clinicians use naloxone as well as nitroprusside infusions as an effective medication to counter the effect of methylergometrin maleate toxicity (2)(3)(4)(5); thus, admission to a tertiary NICU unit is paramount.

Encephalopathy has been observed frequently in the cases reported since the 1960s. Lethargy alternates with agitation, and seizures are noticed as well. (1)(2)(5) Although we did not find any evidence of radiologic brain changes throughout the reviewed cases, brain edema changes were captured on initial head ultrasonography in our patient.

Cardiovascular system and ECG monitoring are not well appreciated, to our knowledge; however, we found that a prolongation of QT interval could be due to methylergometrin intoxication (needs thorough scrutiny).

CPK is markedly increased initially then declines along with clinical improvement; however, CPK level is not well elaborated in the other case studies.

Feeding intolerance, peripheral circulation abnormalities, oliguria, and death have been reported, (1)(2)(3)(4)(6) but these hazards were not noticed in the current case.

Clinical manifestations in our neonate were mild compared with other reported cases, which confirms our belief that these manifestations may be dose dependent. This is because in other cases, patients who received doses ranging from 0.1 mg to 0.5 mg required more aggressive support. (2)(5)(7) A literature review shows that age and route of administration could play a significant role in the variations in clinical presentation among patients. (3)(6)

Management

Supportive care and close observation as well as monitoring of vital signs are adequate during admission.

Patient Course

The patient's overall vital signs were maintained throughout his NICU stay (6 days). Feeding was started after 24 hours, initially by orogastric tube for 2 days then by breastfeeding, and he did not need any respiratory support. Tone, power, pupils' reactivity to light, and reflexes began to improve after the first day of admission, and the neonate recovered completely after 72 hours of age. Brain magnetic resonance imaging findings before discharge were normal.

Lessons for the Clinician

- Medication errors are considered one of the leading causes of morbidity and mortality, therefore notifications about their occurrence are essential for tackling the hazards. These errors could be minimized by a well-written protocol, raising the awareness of medication safety and proper administration, and clarifying policy, as well as adhering to senior staff supervision.
- Respiratory compromise and encephalopathy are by far the most frequent manifestations of methylergometrin maleate toxicity. The aggressiveness of medical support is believed to be directly proportional to the dose given.
- Electrocardiographic changes in the form of prolonged QT intervals as well as elevated creatinine phosphokinase might be considered as a sign of methylergometrin maleate intoxication.
- Admission to NICU is guaranteed to a patient who experiences methylergometrin maleate toxicity.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- For therapeutic drugs commonly used in the neonate (eg, opiates, methylxanthines, barbiturates, etc), know indications for their use, clinical effects, side effects, and toxicity.

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Case 1: The Impact of Methylergometrin Maleate Toxicity on Neonates

Ahmed Badawy, Mohamed Darwich and Ali Aqeel

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2 Feeding Intolerance Following Topical Atropine Instillation in a Premature Infant

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AUTHOR DISCLOSURE Drs Lanlokun, Capriolo, Alexander, and Sundararajan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An extremely low-birthweight female newborn, weighing 545 g, is born at 23 weeks of gestation via cesarean section. Following a pregnancy complicated by preterm labor with prolonged rupture of membranes and positive maternal group B *Streptococcus* status, the newborn requires positive pressure ventilation, chest compressions, intubation, and surfactant administration in the delivery room. After initial stabilization, she is admitted to the NICU. She receives continuous positive pressure ventilation on day 37 after birth and is ultimately weaned to room air. She initially receives enteral feeds with breast milk and gradually advances to full enteral feeds by day 40 after birth. Within a week of tolerating full enteral feeds, she makes a transition to 24 kcal/oz of formula because of insufficient maternal breast milk supply. Her eyes are regularly screened for retinopathy of prematurity (ROP) from 31 weeks' postmenstrual age (PMA). Before each ROP screening, she receives cyclopentolate/phenylephrine and proparacaine ophthalmic eye drops. Her initial eye examination reveals bilateral zone 1 stage 1 ROP. After the diagnosis of bilateral zone 2 stage 3 ROP with plus disease is made at PMA of 36 weeks, she is successfully treated with laser ablation therapy to the peripheral avascular retina of both eyes after a brief period of having nothing orally for 4 hours. Her enteral feeds are resumed later on the same day after laser surgery. She is subsequently started on daily ophthalmic 0.5% atropine drops and tobramycin/dexamethasone ophthalmic drops 4 times a day. On postoperative day 1, she is noted to have tachycardia with pulses ranging from 190 to 200 beats/min 1 hour after ophthalmic atropine is applied. She continues to have intermittent tachycardia, but enteral feeds are continued as she continues to have normal physical examination findings.

DISCUSSION

Progression

On postoperative day 3 (94 days after birth), approximately 12 hours after the application of atropine ophthalmic drops, the infant developed hematochezia, increased abdominal distention, diffuse tenderness, and absent bowel sounds. Enteral feeds were discontinued, and she was started on intravenous fluids, intravenous piperacillin/tazobactam, and vancomycin therapy after drawing blood for bacterial blood culture, complete blood cell count, manual differential count, basic metabolic panel, and lactate. An initial abdominal radiograph reveals "mild diffuse gaseous distention of bowel" (Fig 1A).

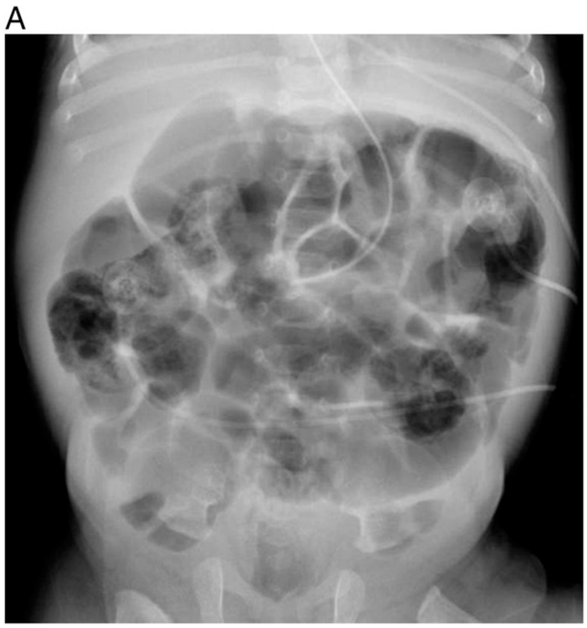

Figure 1A. X-ray of the abdomen at the time of initial symptoms of abdomen distention and hematochezia

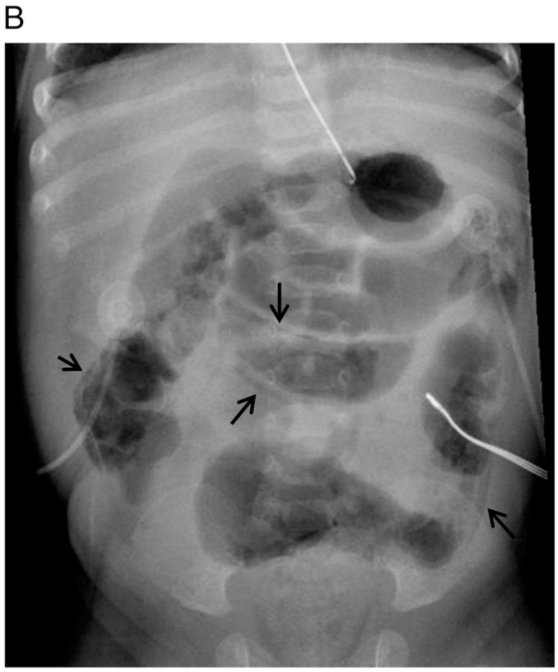

Figure 1B. X-ray of the abdomen approximately 9 hours after onset of hematochezia. Black arrows highlight areas of pneumatosis intestinalis.

The differential diagnosis for this clinical presentation in a neonate includes, but is not limited to, infectious enterocolitis, neonatal appendicitis, cow milk protein allergy, food protein induced enterocolitis syndrome (FPIES), Hirschsprung disease, malrotation with obstruction, intestinal perforation, and late-onset neonatal sepsis. Neonatal appendicitis is extremely rare but can present with abdomen distention, and an abnormal bowel gas pattern on radiography. However, it would also be expected to show air-fluid levels. Allergic colitis including cow milk protein allergy or FPIES would be unlikely in a patient who had been previously tolerating feeds without other signs such as vomiting, diarrhea, and eosinophilia. Hirschsprung disease typically presents with a history of failure to pass meconium within the first 48 hours after birth in addition to the findings of abdominal distention, constipation, and feeding intolerance. Malrotation with obstruction, intestinal perforation, and neonatal sepsis can be associated with feeding intolerance, especially in a patient with hemodynamic instability.

Diagnosis

Abdominal radiography revealed pneumatosis intestinalis without evidence of free air or portal venous gas (Fig 1B). These findings, along with the clinical features of feeding intolerance, abdominal distention, and rectal bleeding, were consistent with the diagnosis of a necrotizing enterocolitis (NEC)-like illness. Ophthalmic atropine drops were then discontinued. The infant's laboratory findings remained reassuring without metabolic acidosis, thrombocytopenia, or dyselectrolytemia. Blood culture remained negative for bacterial growth. She completed an intravenous antibiotic

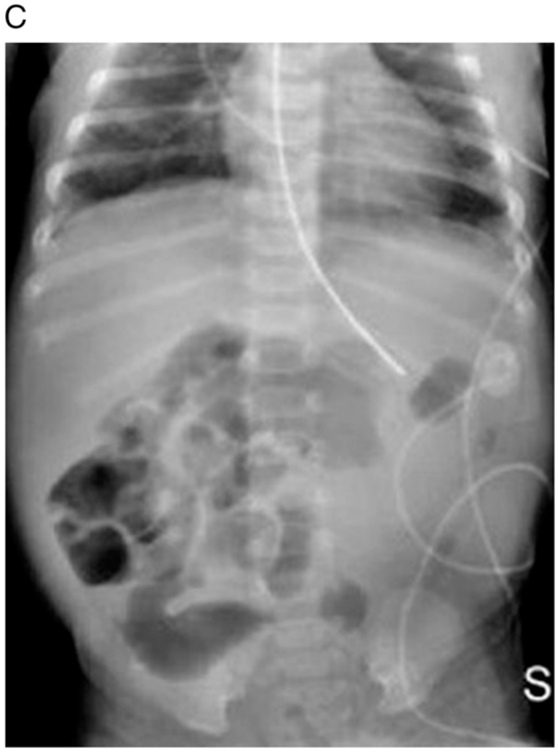

Figure 1C. X-ray of the abdomen following completion of treatment for NEC.

TABLE 1. **Series of Cases of Patients Who Developed Necrotizing Enterocolitis or Paralytic Ileus after Topical Instillation or Oral Administration of Mydriatic Agents**

AUTHOR; YEAR	TITLE OF CASE REPORT	MYDRIATIC DRUG ASSOCIATED WITH PARALYTIC ILEUS	POPULATION	SETTING	OUTCOMES / OBSERVATIONS
Baron-Janaillac et al; (1) 2011	Are mydriatic eye drops dangerous for pre-term infants?	Atropine	Preterm infant	ROP screening	A 6-week-old former 28 week gestation female died from NEC, shortly after receiving eye drops for screening for ROP.
Bauer et al; (2) 1973	Systemic cyclopentolate (Cyclogyl) toxicity in the newborn infant	Cyclopentolate	Premature twins	ROP screening	Both twins developed feeding intolerance, but one twin died from NEC complicated by an intestinal perforation.
Beatson; (3) 1982	Atropine and paralytic ileus	Atropine	Geriatric patient	Enteral atropine for treatment of sialorrhea	A 77-year-old male with Parkinson's disease developed paralytic ileus while being treated with oral atropine for sialorrhea.
Lim et al; (4) 2003	Transient paralytic ileus following the use of cyclopentolate-phenylephrine eye drops during screening for retinopathy of prematurity	Cyclopentolate-phenylephrine	Preterm infants	ROP screening	6-week old former 26 week and 25 week premature infants developed paralytic ileus within 8 hrs following topical cyclopentolate-phenylephrine administration.
Oyachi et al; (5) 2003	Development of ovine fetal ileal motility: Role of muscarinic receptor subtypes	Atropine	Animal model-bovine fetal gut	In vitro study of effects of bethanechol (muscarinic agonist) and antagonists (atropine) on ovine fetal GI muscle contractility	Anticholinergic effect of atropine on the ovine GI muscle was noted to be inhibitory in an age-dependent manner.
Ozgun et al; (6) 2014	Fatal necrotizing enterocolitis due to mydriatic eye drops	Cyclopentolate, tropicamide, phenylephrine	Preterm infant	ROP screening	4 hrs after administering mydriatic drops for ROP screening, a 6-week-old infant developed abdominal distention that progressed to surgical NEC and later died 24 hrs post-operatively.
Princelle et al; (7) 2013	Systemic adverse effects of topical ocular instillation of atropine in two children	Atropine	Pediatric patient	Emergency department	A 6-month-old male presented to the ED with acute onset of urinary retention lasting 36 hrs, after administration of atropine eye drops. A 2-year-old boy developed dry mouth, thirst, and drowsiness within 30 mins of receiving atropine eye drops.

course for 7 days, with significant improvement in her serial abdominal examination findings and radiologic resolution of pneumatosis intestinalis (Fig 1C) without surgical intervention. Enteral feeds were resumed after bowel rest and total parenteral nutrition for 7 days. She advanced to full-volume enteral feeds of 22 kcal/oz and transitioned to all oral feeds by 108 days of age.

The infant continued to receive cyclopentolate/phenylephrine and proparacaine ophthalmic drops for follow-up eye examination with neither vital sign changes nor clinical instability noted. Eye examination before discharge from the NICU showed zone 2 stage 0 bilateral ROP without plus disease. She continued to gain weight adequately and was discharged from the hospital at 117 days of age. Outpatient follow-up visits with pediatric ophthalmology confirmed continued resolution of ROP.

The Condition

NEC, a potentially devastating gastrointestinal emergency, and ROP, a preventable cause of blindness, are common morbidities affecting premature infants. Unlike pathogen-associated NEC, no specific definition exists for NEC-like illness associated with extreme prematurity and delayed feeding. NEC-like illnesses may be associated with intestinal immaturity, altered gut microbiota, delayed initiation or rapid advancement of enteral feeds. ROP has been associated with prematurity, low birthweight and hyperoxia states. In 1973, Bauer et al reported the sentinel case highlighting an association between increased systemic level of cyclopentolate used for ROP screening and a fatal case of surgical NEC. (2)

The use of atropine eye drops is thought to have played a role in the development of a NEC-like illness in our patient. Atropine is an anticholinergic drug often used as a mydriatic agent. Drainage of the drug via the nasolacrimal duct leads to systemic absorption and ultimately, decreased gastrointestinal (GI) tract peristalsis. Authors of prior case reports (Table 1) have hypothesized that premature infants are at risk of developing NEC from the adverse GI side effects of the mydriatic agent in addition to its effects on heart rate and blood pressure (8) and its half-life of approximately 13 to 38 hours. (1) Paralytic ileus has been described in association with atropine use in older patients as well. (3)

Oyachi et al evaluated the development of cholinergic receptors in the GI tract of sheep as a means of postulating the receptor subtypes present in neonates. (5) The study was based on the knowledge that muscarinic receptors play an important role in the physiology of the adult GI tract and that peristalsis is controlled by the parasympathetic and enteric nervous system. (5) An age-dependent increase in response to the anticholinergic activity of atropine in neonatal (7±1 day old lambs) GI tissue compared to that of the fetus was observed. The most notable effect was seen in the adult GI tract, suggesting possible age-dependent changes in receptor subtypes. One can, therefore, postulate that the later development of a NEC like illness in this previously hemodynamically stable infant who was tolerating full enteral feeds may have been affected by maturation of the GI tract, leading to increased sensitivity to the effects of atropine.

Ophthalmic atropine preparation is administered at a variety of concentrations ranging from 0.3% to 1%. (9) A reduction in the drop volume of cyclopentolate is associated with fewer adverse events, with a near equivalent effective pupil dilation. (10)(11) Withholding enteral feeds for 4 hours after ophthalmological examination, decreasing the drop size, and occlusion of the nasolacrimal system after instillation of mydriatic eye drops are some measures which could reduce the incidence of systemic absorption and resulting feeding intolerance. (12)(13)(14) There exists a significant knowledge gap in the literature regarding safety and pharmacokinetic data of topical atropine use in premature newborns that could be addressed with future research. Further study is warranted to characterize possible causation of a NEC like illness secondary to the systemic paralytic effects following topical atropine use.

Lessons for the Clinician

- It is important for the clinician to recognize unexplained tachycardia post-atropine instillation in a premature infant.
- Worsening vital signs and feeding intolerance can be observed as early as 24 hours after administration of atropine ophthalmic drops.
- After initial evaluation aimed at excluding infection, clinicians caring for neonates must be aware of systemic paralytic effects following topical atropine use.
- Neonates must be monitored for feeding intolerance and development of a NEC like illness following topical mydriatic application, both during the screening and following treatment for retinopathy of prematurity.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the differential diagnosis, diagnostic and laboratory features, and approach to management of infectious enteritis and colitis in the neonate.

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Case 2: Feeding Intolerance Following Topical Atropine Instillation in a Premature Infant

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3 Refractory Seizures Continuing into Infancy in a Term Neonate with Definite History of Perinatal Asphyxia

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PRESENTATION

AUTHOR DISCLOSURE Drs Ramaswamy, Rao, Jalan, and Suryanarayana and Mr Kumar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A 7-day-old neonate presents to our NICU with multiple jerky movements of both upper and lower limbs and floppiness. He is the product of a third-degree consanguineous marriage and is born in a peripheral institution. He has a sister who is 6 years old and is healthy.

Birth to 7 Days after Birth

The neonate is born vaginally and requires bag and mask ventilation for 5 minutes. He is transferred to a level II NICU, where he stays for 5 days. He exhibits features of encephalopathy and also has a multifocal clonic seizure 2 hours after birth; he receives a single loading dose of phenobarbital. He is diagnosed as having hypoxic-ischemic encephalopathy (HIE) grade 2. Subsequently, his sensorium improves and he is discharged while breastfeeding exclusively. Since day 6, he has been having multiple episodes of multifocal clonic seizures and is brought to our NICU on day 7.

Day 7 to Day 23

A strong suspicion of neurometabolic disorder arises in view of consanguinity and refractory seizures. He is nil per os. He requires full loading doses of antiepileptic drugs (AEDs) phenytoin and phenobarbital, after which his seizures stop. Testing for blood glucose, arterial lactate, pH, serum ammonia, urine ketones, and urine-reducing substances and tandem mass spectroscopy for inborn errors of metabolism such as aminoacidopathies and fatty acid oxidation defects all have normal results. Lumbar puncture reveals no meningitis. Magnetic resonance spectroscopy shows hypoxic-ischemic changes. Amplitude integrated electroencephalography (EEG) shows periodic epileptic waveforms with a normal interictal background pattern. Electrographic seizure control is noted after phenytoin loading. Urine and cerebrospinal fluid (CSF) pipecolic acid levels are elevated. Pipecolic acid level in CSF is 13.16 μmol/L (reference range, 0.01–2.00 μmol/L), and in urine is 451.75 μmol/mmol of creatinine (reference range, 0.55–24.1 μmol/mmol of creatinine). Pipecolic acid levels are estimated using gas chromatography/mass spectrometry with the selective ion monitoring method using full calibration for both the substances. The neonate receives oral pyridoxine at 30 mg/kg per day in 3 divided doses. EEG changes normalize in the next

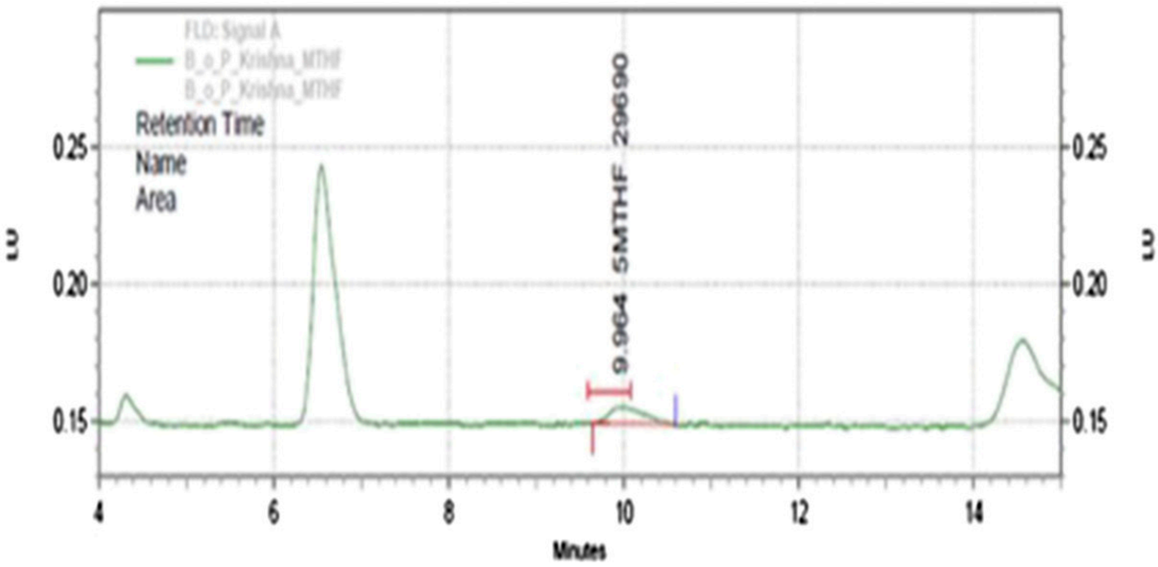
24 hours, sensorium improves, and other AEDs are discontinued in the next 3 days. The neonate is discharged on day 23.

Day 45 to Day 52

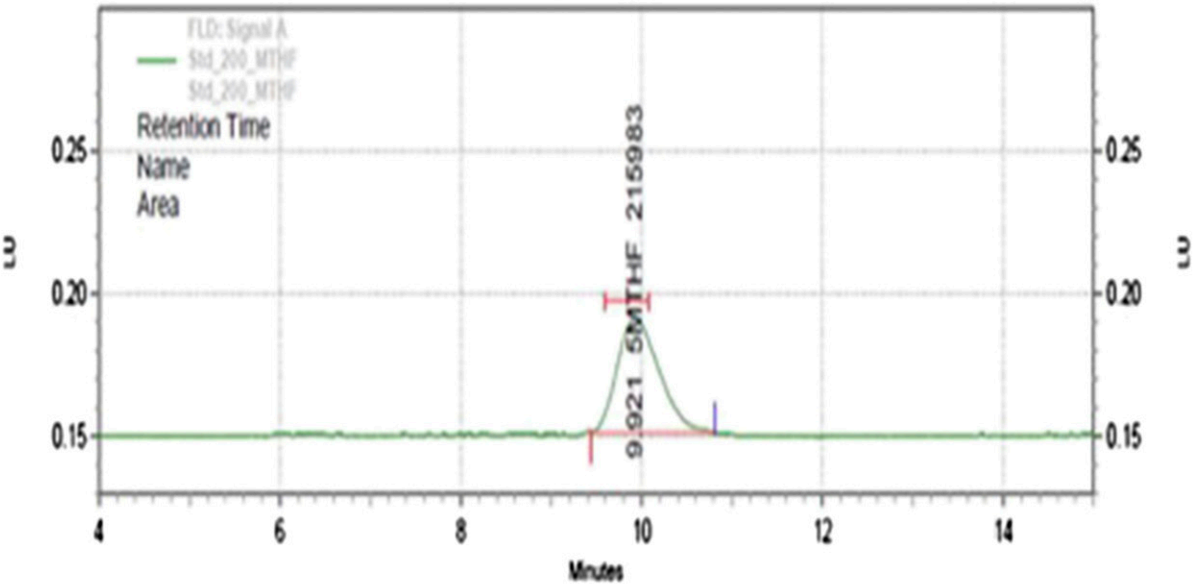
The neonate experiences seizures again on day 45. Further evaluation reveals CSF 5-methyl tetrahydrofolate (5-MTHF) levels to be very low (10.04 nmol/L; reference range, 60-129 nmol/L). CSF 5-MTHF levels are estimated using ultra high-performance liquid chromatography with fluorescent detector (Fig). After folinic acid supplementation, the seizures stop. Presently he is 5 months old, undergoing follow-up evaluations, and receiving pyridoxine and folinic acid treatment. His current developmental age is 3 months with global developmental delay being noted.

DISCUSSION

This was a classic case of folinic acid-responsive seizures (FARS), which are biochemically and genetically similar to pyridoxine-dependent epilepsy (PDE). (1) The initial



Patient Chromatogram



Standard Chromatogram

Figure. Cerebrospinal fluid 5-methyl tetrahydrofolate levels, as estimated using ultra high-performance liquid chromatography.

diagnosis was HIE, which was later changed to PDE. Despite extensive investigations, as well as the fact that the neonate was symptomatic since day 1 after birth, the final diagnosis of FARS was made 45 days after birth. This demonstrates the difficulty in making a rapid diagnosis in cases of PDE and FARS.

First Diagnosis

The first diagnosis of HIE grade 2 was relatively straightforward. The fact that the first seizure responded to a single loading dose of phenobarbital was not surprising because PDE has a varied presentation and can respond to AEDs. Also, PDE can mimic asphyxia. (2) To our knowledge, FARS mimicking asphyxia has not been reported in the literature.

Second Diagnosis

The second diagnosis of PDE was made after the urine and CSF pipecolic acid were found to be elevated. The clinical and electrographic response of seizures confirmed the diagnosis of PDE. In a case report of FARS by Gallagher et al, all of their patients were identified in the neonatal period, 1 responded completely to pyridoxine, 1 had a partial response, and 1 had an initial response followed by recurrence, as seen in the current case. (3) Almost all of them achieved seizure control after folinic acid supplementation.

Final Diagnosis

The final diagnosis of FARS was made after the CSF 5-MTHF levels were measured. The full response to folinic acid supplementation further confirmed the diagnosis.

FARS and PDE are 2 easily treatable neurometabolic conditions that present in the neonatal period. (4) FARS was first reported in 1995 and many case reports were subsequently published. (5) The biochemical and genetic abnormality is exactly the same as that of PDE. The only additional abnormality is the CSF folate deficiency. The mechanism resulting in this folate deficiency in PDE is unknown. This should not be confused with other congenital folate deficiency disorders in which the other biochemical abnormalities of PDE, such as high pipecolic and α-aminoadipic acid levels in CSF and urine, will not be present. (6) Also, these congenital abnormalities of folate deficiency are not known to present in the neonatal period. The long-term prognosis of PDE and FARS is poor, even in treated cases, but delay in supplementation can only make it worse. (3)

Lessons for the Clinician

- Pyridoxine-dependent epilepsy (PDE) and folinic acid-responsive seizures (FARS) can masquerade as perinatal asphyxia and hypoxic-ischemic encephalopathy (HIE). A high degree of suspicion should be maintained in a neonate with HIE who has breakthrough seizures in the neonatal and early infancy period, because seizures related to HIE resolve during this period.
- All cases of suspected neurometabolic disorders should be evaluated for both FARS and PDE. Folinic acid supplementation along with pyridoxine supplementation should be used in all suspected cases until definitive reports are available.
- Partial response to pyridoxine supplementation or recurrence in an already diagnosed case of PDE warrants the addition of folinic acid until cerebrospinal fluid 5-methyl tetrahydrofolate levels are available.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Differentiate asphyxia from other causes of depression at birth, including drug effects and hypovolemia.

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Could Herpes Meningocephalitis Have Been Prevented in this Infant?

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AUTHOR DISCLOSURE Dr Sims has disclosed that she has been compensated for reviewing records and providing testimony in some of the cases highlighted in Legal Briefs. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A 14-day-old female infant born at term was brought to the pediatrician because her right eye was slightly swollen and had a watery discharge. The mother stated that she had an unremarkable pregnancy and vaginal delivery. The records reflected that the infant was healthy at the time of the 48-hour discharge. The physician concluded that a tear duct obstruction was present and asked the parents to massage it. ***The pediatrician retained by the plaintiff explained that an evaluation of the eye with cultures should have been done. The plaintiff explained that in the past, infants with*** **Neisseria gonorrhoeae** ***conjunctivitis presented at 2 to 5 days of age, but partial suppression by ocular prophylaxis has altered the onset to a later time.*** **Chlamydia trachomatis** ***conjunctivitis typically appears 5 to 14 days after birth. Herpes simplex virus (HSV) conjunctivitis was also an important infection to consider because of potentially devastating consequences if not recognized, especially with the eye being a common portal of entry and site of viral replication. The pediatrician retained by the defense disagreed and stated that it was not standard of care to perform a culture on the discharge, given this infant's clinical findings.***

Four days after the pediatrician visit, the mother brought her infant to the emergency department (ED) because of an elevated temperature of 100.5°F (38.1°C). The mother said that an aunt had a cold sore on her mouth when visiting the infant, but no other history of infection was noted at home and the mother again said that her pregnancy was unremarkable. In the ED, the infant's temperature was 101.5°F (38.6°C). Except for an elevated heart rate of 175 beats/min and periorbital swelling of an erythematous right eye that had a watery discharge, the infant's examination findings were normal. Two hours after arrival at the ED, a complete blood cell count (CBC), C-reactive protein (CRP) measurement, bacterial eye culture, blood culture, urine culture, and chest radiography were performed. The CBC was unremarkable and the CRP was less than 7 mg/L (67 nmol/L; reference range, <20 mg/L [190 nmol/L]). A lumbar puncture performed 4 hours after arrival at the ED showed the following results: glucose 45 mg/dL (2.5 mmol/L), protein 0.112 g/dL (1.12 g/L), red blood cell (RBC) count of $2.5\times10^6/\mu L$ ($2.5\times10^{12}/L$), and a white blood cell (WBC) count of $250/\mu L$ ($250\times10^9/\mu L$) with 20% polymorphonuclear leukocytes and 80% monocytes. The treating physicians concluded that the cerebrospinal fluid (CSF) results were normal and the bloody appearance of CSF made it consistent with a traumatic tap. ***The pediatrician retained by the plaintiff agreed that the CSF was consistent with a traumatic tap, but explained that a polymerase chain reaction (PCR) for HSV should have been performed on the CSF, blood, and eye drainage, and an eye culture for herpes should have been performed if the CSF PCR was positive for herpes.***

The infant was admitted to the pediatrics department 10 hours after admission to the ED. The infant was started on treatment with ampicillin and cefotaxime.

The plaintiff pediatrician pointed out that acyclovir should have been empirically started. The defense pediatrician disagreed, pointing to the excessive expense of routinely conducting this evaluation and a low yield of HSV infections in newborns. The nursing and physician notes reflected normal behavior and physical examination findings until the 5th day after admission, when the infant had tonic-clonic seizures. Phenobarbital was administered. Cranial ultrasonography findings were negative. The infant was then transferred to a higher level medical center. Immediately on admission to this referral center, a second lumbar puncture was performed, which showed an RBC count of $1.3\times10^6/\mu L$ ($1.3\times10^{12}/L$) and WBC count of $210/\mu L$ ($210\times10^9/L$) with a predominance of lymphocytes and monocytes. The CSF protein was 2.4 g/dL (24 g/L) and the glucose was 45 mg/dL (2.5 mmol/L). Empirical treatment with acyclovir was started. The result of HSV PCR 1 testing on CSF was negative and the result of HSV PCR 2 testing was positive. The following day, computed tomography (CT) of the brain was performed, which showed large areas of intraparenchymal hemorrhage, suggestive of hemorrhagic encephalitis, consistent with a viral infection. On follow-up at 5 years of age, the child had cerebral palsy, delayed milestones, ongoing seizures, and a behavioral disorder. The case settled without going to trial.

DISCUSSION

The initial presentation of HSV central nervous system (CNS) disease may be indistinguishable from other causes of neonatal sepsis or meningitis and the consequences of delayed treatment for HSV are high morbidity and mortality. Therefore, HSV should be considered in the differential diagnosis of sick neonates. It is especially important to consider HSV as a causative agent in neonates with fever (especially within the first 3 weeks after birth), a vesicular rash, or abnormal CSF findings. Because the presentation is generally nonspecific, a high index of suspicion should prompt the clinician to consider HSV early in the evaluation. Proactively investigating and beginning acyclovir treatment is effective if administered early in the course.

The incidence of neonatal HSV infection in the United States ranges from 1 in 2,000 to 1 in 3,000 live births. An estimated 1,500 cases of neonatal HSV infection are seen annually in the United States.

Neonatal HSV is acquired in 3 distinct periods: the intrauterine, perinatal, and postnatal periods.

- **Intrauterine HSV** occurs rarely (1 in 250,000 deliveries). It results from maternal primary HSV infection and viremia during pregnancy. It is associated with placental infarcts, necrotizing calcifying funisitis, hydrops fetalis, and fetal demise. Survivors of in utero HSV may exhibit skin vesicles, ulcerations, or scarring; eye damage; and severe CNS manifestations, including microcephaly and hydranencephaly. Intrauterine infection may also be secondary to an ascending infection after prolonged rupture of membranes in pregnant women with active HSV infection near the time of delivery. Ascending transplacental infection of the fetus may also occur through intact amniotic membranes.
- **Perinatal HSV** comprises most cases of neonatal HSV when HSV is present in the genital tract of a pregnant woman at the time of delivery. The woman may or may not be symptomatic and most commonly, a history of HSV is negative. Perinatally acquired HSV is categorized into 3 main groups for therapeutic and prognostic considerations:
  - Localized to the skin, eye, and mouth (SEM)
  - Affecting the CNS with or without SEM involvement
  - Disseminated disease

  There is some overlap in these categories.
- **Postnatal HSV** infection occurs in 10% of neonatal HSV infections. It occurs when a caretaker with active HSV infection has close contact with the newborn.

Approximately one-third of neonatal HSV involves the CNS, which may occur as a result of localized retrograde spread from the nasopharynx, olfactory, or ocular nerves to the brain or through hematogenous spread. HSV CNS disease, also called *neonatal HSV meningocephalitis*, usually presents in the second or third week. Clinical symptoms of HSV CNS disease are nonspecific and include temperature instability, poor feeding, lethargy, irritability, and later seizures. Early in the course, the infant may appear asymptomatic. CSF analysis of HSV CNS disease typically shows a mononuclear cell pleocytosis, normal or moderately low glucose concentration, and mildly elevated protein levels; CSF studies may be normal early in the course of the illness. RBCs are not significantly affected in neonatal HSV CNS disease. In the past, elevated RBCs in the CSF suggested HSV, but this finding probably reflects a relatively more advanced HSV disease—hemorrhagic HSV encephalitis—which is no longer frequently seen because of improved diagnostic capabilities.

The diagnosis of neonatal HSV disease requires sampling of multiple sites:

- HSV surface cultures and PCR testing should be performed on swabs of the infant's conjunctivae, nasopharynx, and rectum. Viral culture is the test of choice for detecting HSV in surface specimens. Surface cultures are positive in more than 90% of cases and provide the greatest diagnostic yield of all methods to detect HSV, regardless of disease classification. Positive cultures in specimens obtained from these sites more than 12 to 24 hours after birth indicate viral replication and suggest infection, rather than contamination from intrapartum exposure.

- Culture and PCR testing should be performed on specimens of skin vesicles.
- CSF specimens should undergo PCR testing for HSV; all neonates with suspected HSV, even infants who appear to have isolated SEM disease, should undergo a lumbar puncture because clinical findings may be absent early in the course of CNS disease. PCR is the test of choice for detecting CNS involvement and has a sensitivity of 75% to 100% and specificity of 71% to 100%. Viral culture of CSF sample is less sensitive (25%-40%).
- Whole blood should undergo PCR testing for HSV.
- Alanine aminotransferase should be measured as an indicator of hepatic involvement.

Affected infants often have an abnormal encephalogram early in the course. CT and magnetic resonance imaging scans may be normal initially, but several days to a week into the illness, neuroimaging may show parenchymal brain edema, hemorrhage, or destructive lesions. With the advent of antiviral therapy, all forms of HSV disease have dramatically improved outcomes.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the management of an infant born to a mother with active genital herpes lesions or with a history of genital herpes infection.
- Know the epidemiology, prevention, and pathogenesis of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella zoster.
- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster.

Suggested Readings

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Legal Briefs: Could Herpes Meningocephalitis Have Been Prevented in this Infant?

Maureen E. Sims

NeoReviews 2018;19;e773
DOI: 10.1542/neo.19-12-e773

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Preeclampsia in a Monochorionic-Diamniotic Twin Gestation

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

AUTHOR DISCLOSURE Drs Dieffenbach and Young have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. Arterial Umbilical Cord Gas Values

	pH	Pco_2 (mm Hg)	Po_2 (mm Hg)	Base Excess
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤−10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤−10
Metabolic acidosis	<7.20	<60	Variable	≥−10
Mixed acidosis	<7.20	>60	Variable	≥−10

*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695.

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles/min, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

  Absent: Amplitude range is undetectable
  Minimal: Amplitude range is greater than undetectable to 5 beats/min
  Moderate: Amplitude range is 6–25 beats/min
  Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes

  o Normal: ≤5 contractions in 10 minutes
  o Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:

  —Baseline rate: 110 to 160 beats/min
  —Baseline FHR variability: Moderate
  —Late or variable decelerations: Absent
  —Early decelerations: Present or absent
  —Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:

  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - ▪ Recurrent late decelerations
    - ▪ Recurrent variable decelerations
    - ▪ Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112:661–666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

A 33-year-old gravida 1 woman was seen at 33 weeks, 6 days of gestation with monochorionic-diamniotic twins. She had gestational hypertension and was admitted to the antepartum service for evaluation of preeclampsia in the setting of newly elevated blood pressures and proteinuria. Her medical history was unremarkable; she had a normal prepregnancy body mass index. Her pregnancy was notable for a spontaneous monochorionic-diamniotic twin gestation for which she received close maternal and fetal monitoring. Fetal surveillance had been unremarkable, with appropriately grown twins without evidence of twin-twin transfusion syndrome or twin anemia polycythemia sequence.

CASE PROGRESSION

The day before this presentation, the patient had been diagnosed with gestational hypertension, with blood pressures in the mildly elevated range (140-150/70-90 mm Hg) as noted in the office. The remainder of her vital signs were within normal limits, with a heart rate of 99 beats/min, temperature of 98.2°F (36.8°C), and respiratory rate of 16 breaths/min. She was asymptomatic on initial evaluation, with no headache, visual changes, vaginal bleeding, abdominal cramping or contractions, right upper quadrant abdominal pain, significant edema, or leaking fluid. She reported active movement of both fetuses. Laboratory studies did not show any evidence of *h*emolysis, *e*levated *l*iver enzyme levels, *l*ow *p*latelet count (HELLP) syndrome. Recent ultrasonography demonstrated reassuring and concordant growth of both fetuses. The presenting twin was in breech presentation. The patient received an initial dose of betamethasone to reduce the risks of prematurity in the event that iatrogenic preterm delivery was recommended. A nonstress test demonstrated a reactive FHR tracing for each twin; no FHR decelerations were noted. The patient was admitted to the antepartum unit for close maternal and fetal surveillance in the setting of gestational hypertension.

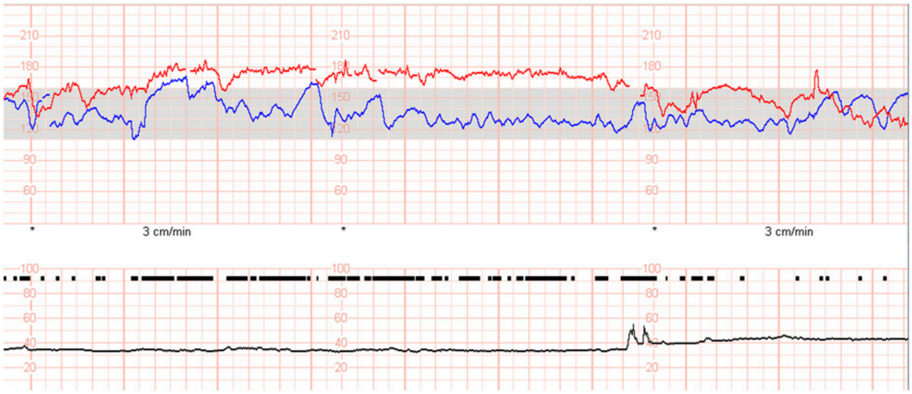

Figure 1. Electronic fetal monitoring strip 1.

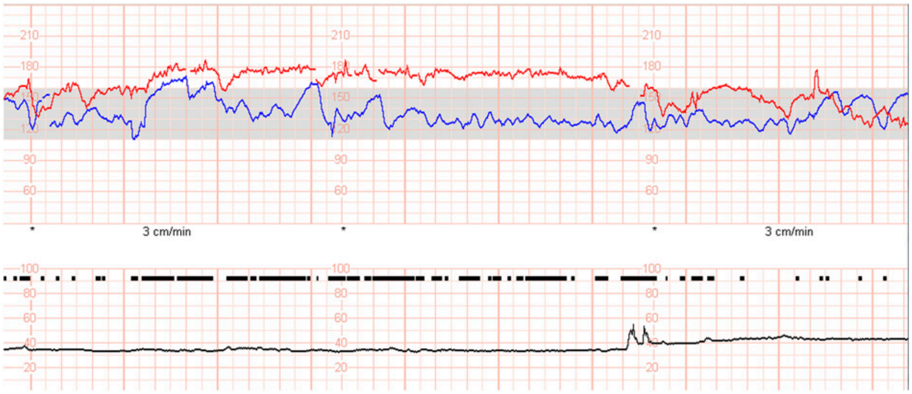

Figure 1. Electronic fetal monitoring strip 1.

Findings from EFM strip 1 are as follows (Fig 1):

- Variability: Twin A moderate; twin B moderate
- Baseline rate: Twin A (red) 130 beats/min (not shown); twin B (blue): 120 beats/min
- Episodic pattern: prolonged acceleration in twin A for 7 minutes
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Category I
- Differential diagnosis: Transient fetal stimulation, fetal anemia, fetal hypoxia, fetal tachyarrhythmia, maternal fever, drug induced, amnionitis
- Action: Expectant management

The patient underwent a 24-hour urine protein collection (570 mg), which confirmed a diagnosis of preeclampsia without severe features. The patient remained hospitalized for blood pressure monitoring and daily fetal monitoring via nonstress tests. She did not develop any symptoms of preeclampsia and her blood pressures remained in a mild range (<160 mm Hg systolic and <110 mm Hg diastolic) without antihypertensive medication.

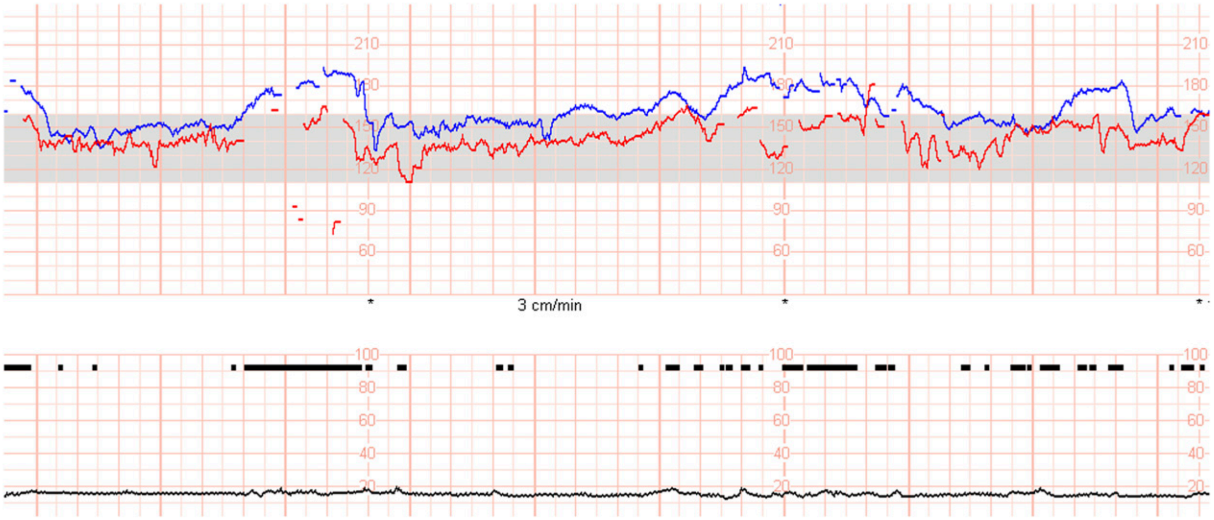

Figure 2. Electronic fetal monitoring strip 2.

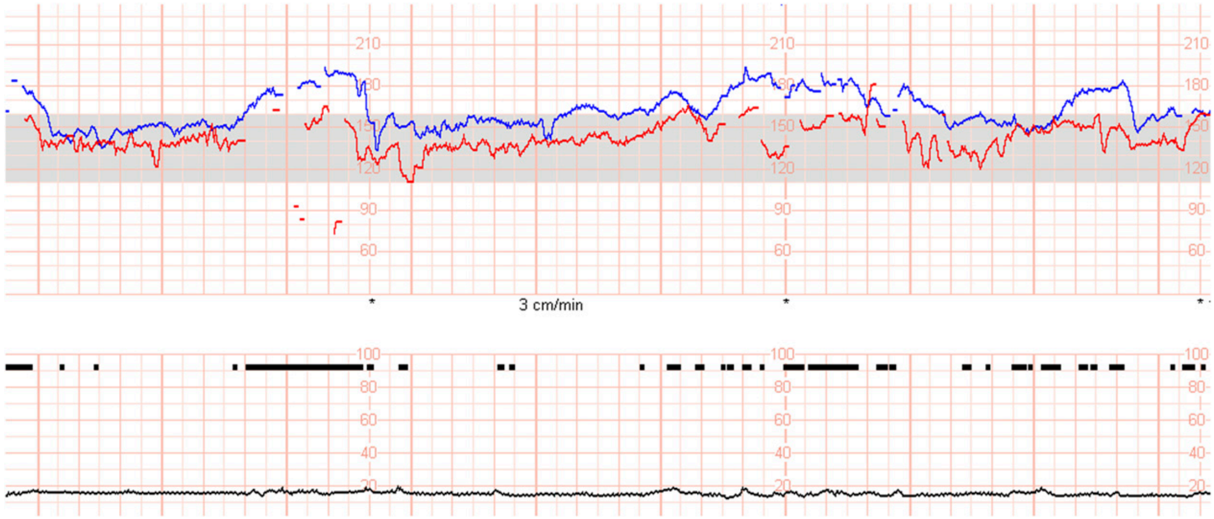

Figure 2. Electronic fetal monitoring strip 2.

Findings from EFM strip 2 are as follows (Fig 2):

- Variability: Twin A moderate; twin B moderate
- Baseline rate: Twin A (red) 130 beats/min; twin B (blue): 140 beats/min
- Episodic pattern: Variable deceleration in twin A lasting 10 seconds
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Twin A category II with variable deceleration; twin B category I
- Differential diagnosis of variable deceleration: idiopathic, cord compression, placental insufficiency
- Action: Expectant management, because twin A and twin B have an overall reassuring assessment with moderate variability, accelerations, and only one brief, nonrecurrent variable deceleration

On hospital day 2 at 34 weeks, 1 day of gestation, the patient developed blood pressures in the severe range of 172/99, 170/104, and 161/100 mm Hg, consistent with a diagnosis of preeclampsia with severe features. She continued to deny headache, visual changes, or abdominal pain. She had no vaginal bleeding or shortness of breath. Given these severe range blood pressures and gestational age, delivery was recommended. The patient was given 10 mg of oral immediate-release nifedipine as a rapid-onset antihypertensive medication and transferred to the labor and delivery department for eclampsia prophylaxis with magnesium sulfate, urgent blood pressure control, and delivery. A cesarean delivery was planned, given the malpresentation of one of the twins. Serum laboratory testing was repeated and results were similar to her initial results. There was no evidence of evolving HELLP syndrome.

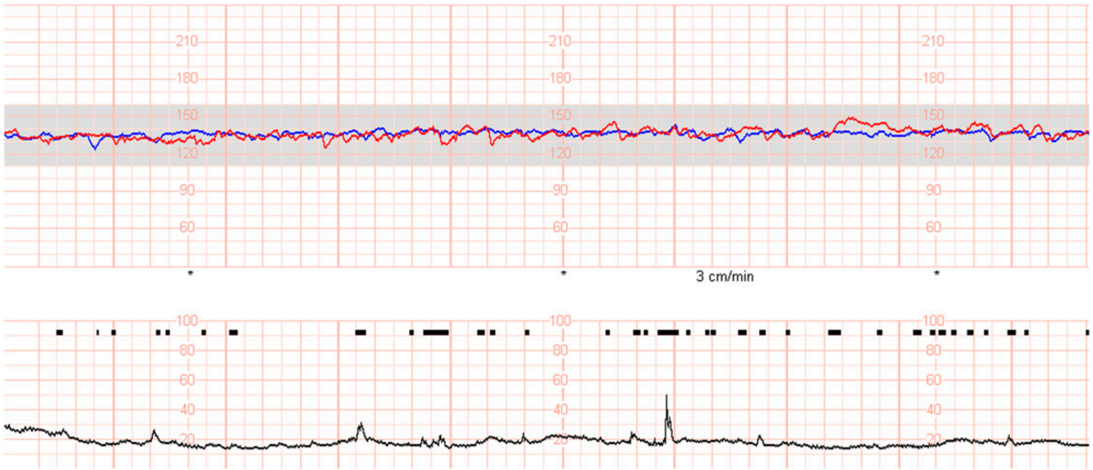

Figure 3. Electronic fetal monitoring strip 3.

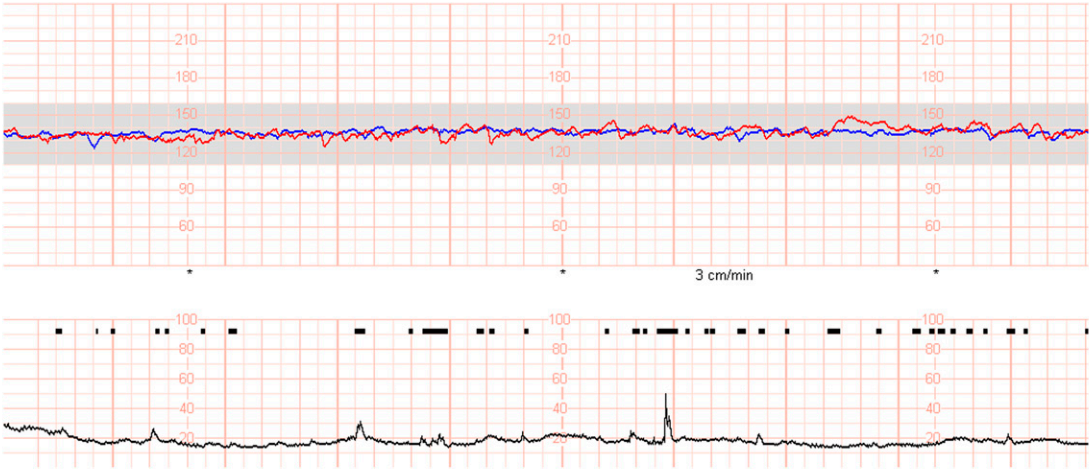

Figure 3. Electronic fetal monitoring strip 3.

Findings from EFM strip 3 are as follows (Fig 3):

- Variability: Twin A moderate; twin B moderate
- Baseline rate: Twin A (red) 130 beats/min; twin B (blue): 130 beats/min
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Category I with moderate variability and no decelerations. The tracing is not reactive, given the absence of accelerations; however, the tracing has a reassuring category I interpretation.
- Differential diagnosis: Fetal sleep cycle, normal variation
- Action: Expectant management currently; if accelerations are absent for a prolonged period, consider obtaining a biophysical profile for further assessment of fetal status. A cesarean delivery was planned in the near future and accelerations had been noted just before this clip.

OUTCOME

The patient underwent an uncomplicated primary cesarean section with delivery of 2 male infants, delivered in breech (twin A) and cephalic (twin B) positions. Apgar scores for twin A were 8 and 9 at 1 and 5 minutes, respectively, and for twin B, were 8, 6, and 8 at 1, 5, and 10 minutes after birth, respectively. The infants were brought to the warmer and dried and neonatal resuscitation assessment was initiated by the NICU team. Twin A demonstrated good tone and a strong cry. He did not require any respiratory support and remained euglycemic throughout his NICU course. Twin B was noted to have good tone and initial cry; however, he developed secondary apnea and a heart rate of 50 beats/min. Positive pressure ventilation was initiated and continued for 2 minutes. He improved and was transitioned to continuous positive airway pressure (CPAP). He was transferred to the NICU on CPAP but then developed increased work of breathing requiring intubation. Chest radiography was performed, and the result was consistent with surfactant deficiency. He was transitioned to room air 1 day after birth and had no further respiratory issues.

The mother's postpartum course was complicated by postpartum hemorrhage requiring administration of multiple uterotonics and surgery to control hemorrhage from uterine atony. She required multiple blood product transfusions, including packed red blood cells, fresh frozen plasma, and platelets for blood loss anemia and consumptive coagulopathy. She had postpartum hypertensive urgency requiring intravenous blood pressure control. Ultimately she recovered well without further complications and was discharged from the hospital on postpartum day 5. Both infants were discharged in good condition 11 days after birth.

DISCUSSION

Multifetal gestations are associated with higher rates of maternal, fetal, and infant morbidity and mortality. (1)(2)(3)(4)(5) Over the last several decades, the number of multiple-gestation pregnancies has notably increased, making these issues more relevant in contemporary practice. Twin pregnancies are associated with significantly higher rates of premature delivery and are at higher risk of stillbirth and neonatal death, compared with singleton pregnancies. (2) On average, twin gestations have a preterm delivery (35–36 weeks' gestation) than the average singleton delivery (39 weeks). (1) Neonates from a twin gestation have a higher likelihood of lower birthweight (approximately 2/3 of twin fetuses delivered will weigh <2,500 g). (1) Maternal risks include an estimated 20% risk of preeclampsia, an increased likelihood of antenatal hospitalization, and iatrogenic preterm delivery, such as in this case. Additional maternal morbidities in a twin gestation include HELLP syndrome, gestational diabetes, cesarean delivery, hemorrhage, nutritional deficiencies, and musculoskeletal concerns. (5)

Chorionicity of a twin gestation is an important component in determining additional risk to a twin pregnancy, because compared with dichorionic twins, monochorionic twins have increased rates of prematurity, fetal growth restriction, and congenital anomalies. A monochorionic twin gestation has the risk of twin-twin transfusion syndrome or twin anemia polycythemia sequence, which are risks exclusive to monochorionic placentation. (2) It is important to establish accurate chorionicity via ultrasonography in the first trimester to appropriately manage the pregnancy and to counsel the patient about the risks involved in the pregnancy.

This patient's pregnancy was complicated by preterm preeclampsia with severe features, and an iatrogenic preterm delivery was recommended. The patient developed severe range blood pressures (>160 mm Hg systolic and/or >110 mm Hg diastolic) requiring urgent blood pressure control. The American College of Obstetrics and Gynecology defines preeclampsia as new-onset hypertension and proteinuria. Preeclampsia may progress to a more severe form, referred to as *preeclampsia with severe features* defined by severe range blood pressure, laboratory abnormalities demonstrating transaminitis or acute renal insufficiency, pulmonary edema or persistent and severe symptoms of headache, scotomata, acute nausea or vomiting, and/or right upper quadrant pain. Women who develop preeclampsia with severe features at a preterm gestation need to be carefully evaluated regarding the timing of delivery to balance the maternal risks of expectant management with the neonatal risks of a premature delivery. Delivery is recommended for women who develop preeclampsia with severe features after 34 weeks' gestation, given the maternal morbidity of ongoing expectant management after this gestational age and the expected reassuring neonatal outcome. (1)

This case demonstrates the maternal and neonatal morbidity associated with a twin pregnancy. This was an otherwise healthy young woman who developed hypertensive disease in pregnancy that required hospitalization, preterm delivery of her infants prompting NICU care, and a postpartum course complicated by hemorrhage treated with surgical intervention and blood product transfusions. Pregnancies with monochorionic-diamniotic twin gestations require appropriate and thorough counseling along with astute recognition and management of any complications that arise.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the types of multiple gestation.
- Know the effects on the fetus and/or newborn infant of mild preeclampsia and its management.
- Know the effects on the fetus and/or newborn infant of severe preeclampsia, including HELLP syndrome, and its management.

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Strip of the Month: Preeclampsia in a Monochorionic-Diamniotic Twin Gestation

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An Infant with Severe Stridor and Cyanosis at Birth

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THE CASE

A male infant born via vaginal delivery presents with biphasic stridor, cyanosis, tachypnea, chest retractions, and copious secretions since birth.

Prenatal and Birth Histories

- The mother is a 22-year-old gravida 2, para 1 woman
- Pregnancy was complicated by polyhydramnios without gestational diabetes mellitus
- Prenatal ultrasonography demonstrated normal anatomy with maximum amniotic fluid index of 39 cm and single deepest pocket of 14.3 cm
- Induced at 37 3/7 weeks' gestation secondary to premature rupture of membranes
- Apgar scores: 5 and 7 at 1 and 5 minutes, respectively
- The pediatrician was called because the neonate had respiratory distress 5 minutes after birth. Positive pressure ventilation was administered with bag and mask for apnea; continuous positive airway pressure (CPAP) was initiated for continued respiratory distress

Presentation

After birth, the infant was noted to have increased work of breathing, severe biphasic stridor, and cyanosis. He was briefly given positive pressure ventilation for apnea, and was then administered CPAP with a fraction of inspired oxygen (F_{IO_2}) of 100%. Multiple attempts at intubation were unsuccessful; a laryngeal mask airway placement was not attempted. The infant was subsequently given high-flow nasal cannula at 3 L/min with an F_{IO_2} of 1 and transported to the NICU at a tertiary hospital. The infant continued to have stridor with significant increased work of breathing, but saturations remained 85% or greater on 3 L/min and an F_{IO_2} of 1. Before transport, a capillary blood gas showed a pH of 7.08 and P_{CO_2} of 89 mm Hg (12 kPa); a chest radiograph was concerning for bibasilar pneumothoraces.

Vital Signs

- Heart rate: 168 beats/min
- Respiratory rate: 53 breaths/min
- Blood pressure 78/35 mm Hg, mean 51 mm Hg
- Temperature: 97.7°F (36.5°C)

Physical Examination (4 Hours after Birth)

- Birthweight: 3,825 g (82nd percentile), length 50.8 cm (55th percentile); head circumference: 37 cm (97th percentile)

AUTHOR DISCLOSURE Drs Kochan, Freiden, Pyle, Isaiah, and Sundararajan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

- Oxygen saturation: 97% (FiO_2 1.0 on 3 L/min nasal cannula)
- Head: Atraumatic; anterior fontanelle open, soft, and flat
- Oral cavity: Moist mucous membranes, palate intact to palpation, tongue normal
- Lungs: Tachypnea, respiratory distress with severe subcostal retractions, and loud, stridulous breath sounds bilaterally, desaturation noted when prone positioning attempted
- Cardiovascular: Tachycardic, regular rhythm, no murmur appreciated
- Abdomen: Soft, decreased bowel sounds, no distention
- Genitourinary: Normal term male external genitalia
- Skin: Pink, warm, capillary refill <3 seconds, pallor
- Neurologic: Lethargic, mild hypotonia

Laboratory Studies

- Arterial blood gas: pH 6.87, PCO_2 >92 mm Hg (12.2 kPa), PO_2 49 mm Hg (6.5 kPa), lactate 11.7 mg/dL (1.3 mmol/L); drawn 4 hours after birth on arrival at referral hospital while infant was receiving 3 L/min high-flow nasal cannula with FiO_2 of 1

Progression

On arrival at the referral hospital, additional intubation attempts were unsuccessful. No intervention was performed for the pneumothorax as depicted in the radiograph in Fig 1 because the size of the pneumothorax decreased on subsequent chest radiography repeated 2 hours later and resolved completely by the next day. Racemic epinephrine was administered without improvement. Prone positioning and laryngeal mask airway placement resulted in desaturation. After consultation with otolaryngology, the infant was taken emergently to the operating room 5 hours after birth for evaluation under general anesthesia.

Differential Diagnosis

- Congenital laryngeal saccular cyst (SC)
- Laryngeal web
- Laryngocele
- Laryngomalacia
- Subglottic stenosis
- Tracheomalacia
- Vocal fold paralysis

Actual Diagnosis

Congenital laryngeal SC

MANAGEMENT

Laryngoscopy showed a large (2×2 cm) right-sided cystic mass as completely effacing the laryngeal inlet by displacing the entire supraglottis (Fig 2A). The cyst was decompressed with a laryngeal needle with removal of approximately 3 mL of turbid fluid. After aspiration, the patient underwent intubation and returned to the NICU. A postoperative capillary blood gas measurement 7 hours after birth while the infant was receiving mechanical ventilation showed a pH of 7.10, PCO_2 of 85 mm Hg (11.3 kPa), and PO_2 of 34 mm Hg (4.5 kPa).

The infant underwent extubation at 31 hours of age. Increasing stridor, work of breathing, and desaturations an hour after extubation necessitated reintubation in the operating room. Under direct visualization, the cyst was noted to have reaccumulated, requiring repeat decompression and marsupialization (ie, cyst converted into an open pouch for continued drainage). After 4 days, the patient underwent successful extubation to CPAP. The rest of his hospital course was complicated by poor oral feeding and continued hoarseness, which improved with time.

After discharge from the NICU, the infant had recurrent symptoms. A repeat upper airway endoscopy in the office demonstrated recurrence of the cyst at 7 weeks of age (Fig 2B). A tracheostomy was performed after admission to the PICU, and further management of the cyst was deferred. At 6 months of age, the infant was noted to have poor tolerance for capping of the tracheostomy preventing airflow through the tube. A repeat endoscopic assessment revealed Cotton-Myer grade II subglottic stenosis, with 51% to 70% obstruction (Fig 2C). (1) The team performed balloon dilation of this region but the infant continued to have significant stridor. A single-stage laryngotracheal reconstruction (ssLTR) was

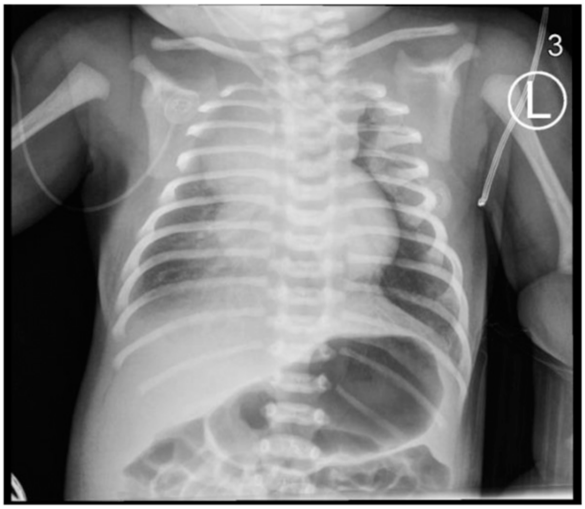

Figure 1. Chest radiograph of infant on arrival at the referral hospital at 5 hours of age. A moderate left pneumothorax is demonstrated, as well as mild streaky perihilar opacities with more focal areas of atelectasis with a small right effusion.

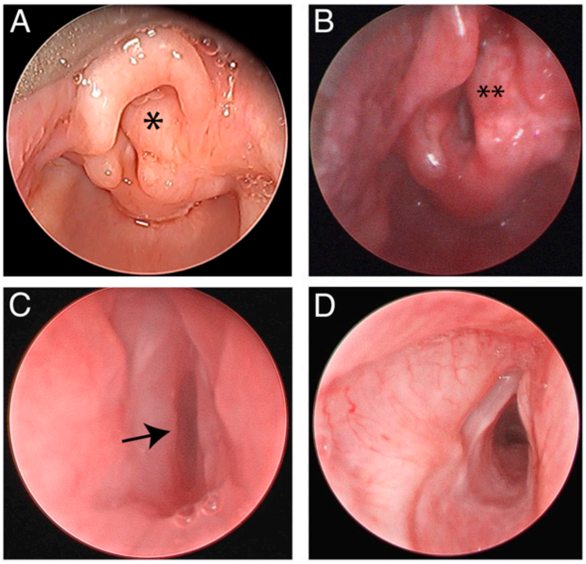

Figure 2. Endoscopic images of the larynx in an infant with a congenital saccular cyst. A. Completely obstructive saccular cyst (*) with no view of the vocal cords. B. Supraglottis after resection of the cyst demonstrating postsurgical scar-related changes (**). C. Slit-shaped subglottis with edema consistent with subglottic stenosis (arrow). D. A patent subglottis following single-stage laryngotracheal reconstruction.

performed at 1 year of age to facilitate decannulation (Fig 2D). Subsequent to the ssLTR, his tracheostomy was removed and the infant did well at home until he was brought to the emergency department with signs of respiratory distress 6 weeks after the procedure. In the operating room, an obstructive granuloma was noted at the site of the graft, which was debrided endoscopically. The infant remained symptom-free for 6 months in room air after the procedure.

WHAT THE EXPERTS SAY

Laryngeal SCs are congenital, fluid-filled lesions that arise from the saccule of the larynx. (2) Congenital laryngeal SCs of the newborn frequently cause severe dyspnea from upper airway obstruction. Emergent management may consist of intubation, decompression, or tracheostomy. (3) Most commonly, these cysts arise between the aryepiglottic fold and the arytenoid cartilage. (4) The saccule is thought to lubricate the vocal folds with secretions from its lumen; congenital or acquired blockage of the drainage pathway from the saccule can lead to cyst formation. (5) The differential diagnosis includes laryngomalacia, laryngocele, laryngeal web, vocal fold paralysis, subglottic stenosis, and tracheomalacia. (4)

Fetuses with an SC can present antenatally with polyhydramnios, particularly if there is complete airway obstruction. Affected infants can present with symptoms beginning at 10 days to 1 year after birth and less commonly, are symptomatic at birth. (6)(7)(8) The incidence ranges from approximately 1.40 to 1.82 per 100,000 live births. (7)(8) The mortality can be as high as 40% when SCs are undiagnosed. (9) Up to 50% of cases, however, are asymptomatic. (10) The initial postnatal presentation may commonly be mistaken for laryngomalacia, which is a common cause of congenital stridor. Key differences include a weak cry in the former. (11) In addition, in cases of lateral congenital laryngeal SCs, symptoms improve with the patient lying on the affected side, as opposed to prone positioning in the case of laryngomalacia. (12)

Although radiographic imaging of the neck can suggest the presence of an SC, direct visualization of the airway is crucial for diagnosis. (12) Laryngomalacia, laryngoceles, webs, vocal cord paralysis, and subglottic stenosis can also be identified with direct laryngoscopy. (4) Endoscopy usually reveals a cystic mass occluding the supraglottic larynx. Aspiration of the cysts yields thick, mucoid material. (4)

Management for infants with SC includes securing the airway with intubation, or tracheostomy in some cases, with subsequent cyst removal. Needle aspiration could confirm the diagnosis and may avoid tracheostomy. With recurrence, endoscopic excision is recommended. (13) Even after excision, the rate of recurrence can be as high at 41%, with most recurrences occurring within 1 to 3 months. (14) After 6 months, recurrence is unlikely. Ultimately, tracheostomy may still be required in up to 65% of affected patients. (13) Surgical treatment has also been associated with acquired subglottic stenosis, which requires airway reconstruction to facilitate decannulation. (15)

CONCLUSIONS

Saccular cysts are rare lesions in infants. The diagnosis of SCs should be considered when evaluating any infant presenting with stridor and signs of upper airway obstruction at birth. The symptoms may improve with positioning the infant on the affected side. Acquired subglottic stenosis can result after surgical treatment of an SC.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the various causes of stridor in the newborn and how to assess severity.
- Know the clinical features of an infant with airway obstruction.
- Plan appropriate diagnostic evaluation and management for an infant with airway obstruction.

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Posterior Urethral Valves: Prenatal, Neonatal, and Long-Term Management: 1. D; 2. C; 3. E; 4. A; 5. B.

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